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CONTENTS

PAGE

The Effect of Forced Feeding on the Nitrogen Equilibrium and the Blood in Pernicious Anemia.
By Herman O. Mosenthal 129

The Clinical Significance of the Irregular Distribution of Various Cells and Parasites in the Blood Stream and the Production of Abortive Leukæmic Changes and of Splenomegaly in the Macacus Rhesus. (Illustrated.)
By Andrew Watson Sellards and Walter Albert Baetjer 135

Memorial Meeting to Dr. Theodore Caldwell Janeway. (Illustrated.) 142

Dr. John Hall: Shakespeare's Son-in-Law. (Illustrated.)
By Eli Moschcowitz, A. B., M. D. 148

Proceedings of Societies.
The Johns Hopkins Hospital Medical Society 152
Demonstration of a Duodenectomized Dog. (Abstract.) [Dr. Ernest G. Gray];—The Origin of the Corpus Luteum [Dr. G. W. Corner];—On the Absorption of Drugs and Poisons from the Vagina. (Abstract.) [Dr. David I. Macht];—On the Absorption of Drugs from the Urethra, Bladder, Ureters and Pelvis of the Kidney. (Abstract.) [Dr. David I. Macht];—Cinq ans Après [Dr. F. C. Shattuck];—Exhibition of a Case of Internal Hydrocephalus [Dr. W. E. Dandy];—Visits to Cantonments. (Abstract.) [Dr. Welch];—A New Hypophysis Operation [Devised by Dr. G. J. Heuer. Presented by Dr. W. E. Dandy, in Dr. Heuer's Absence];—Observations upon the Pathology of Diabetes [Dr. Frederick M. Allen];—Results of Past Methods and To-Day's Problems in the Treatment of Diabetes [Dr. Elliott P. Joslin].
The Johns Hopkins Hospital Historical Club 155
The Historical Section of the Royal Society of Medicine in London. (Extract from Dr. Futcher's Letter to Dr. Hurd, December 16, 1917.)

Notes on New Books 156

Books Received 156

THE EFFECT OF FORCED FEEDING ON THE NITROGEN EQUILIBRIUM AND THE BLOOD IN PERNICIOUS ANEMIA

By Herman O. Mosenthal

(From the Medical Clinic of The Johns Hopkins Hospital)

Forced feeding has always been relied on as an important aid in the treatment of pernicious anemia. This form of therapy is based on the common idea that weak and feeble individuals become healthy and strong if they receive a generous amount of nourishing food. Such a conception has no scientific foundation and yet it is the only one on which the present day use of diet in this disease rests. Prolonged feeding experiments in which the diet has been accurately weighed and calculated are lacking and the skepticism of many physicians in regard to the value of diet in pernicious anemia evidently depends largely upon circumstantial evidence and not upon accurate observations.

If a high diet is to be of benefit to a case of pernicious anemia, it should bring about at least two results: First, there should be an assimilation of protein by the body, or, measured in terms of nitrogen, there should be a positive nitrogen balance; second, the red blood cells and hemoglobin should increase. The present article deals with three cases of pernicious anemia who were put on forced feeding for about one month and studied with the above points of view in mind. It was originally intended to make this work much more extensive, but inasmuch as under the present circumstances it will have to be discontinued indefinitely, the cases observed thus far are reported at this juncture, as they prove certain points in regard to the relation of diet to pernicious anemia.

Some doubt still exists as to whether or not it is possible to effect an assimilation of protein in pernicious anemia and allied conditions. Pearce (1) has recently made the following excellent summary of the status of this question:

From a review of the literature it is evident that in anemia, with or without splenic disease, the majority of investigators have experienced difficulty in obtaining a nitrogen balance. Umber (2), in his study of Banti's disease; Minot (3), in pernicious anemia; McKelvy and Rosenbloom (4), in congenital hemolytic icterus, and Rosenqvist (5), in pernicious anemia and bothriocephalus anemia, all report a pathologic destruction of protein. Umber (6) goes so far as to urge this "toxic destruction" as a

criterion for operation. Von Noorden (7) alone opposes this theory of increased destruction of protein in anemia. In the two cases we report, no difficulty was experienced in obtaining a positive nitrogen balance before operation: feeding was not forced, the patients merely satisfying their natural desires for food. Nevertheless, the increased retention, immediately after the operation, on the same nitrogen intake would appear to support the theory that some toxogenic influence had been removed. To this influence, however, must be added as a cause of retention the higher level of reparative processes going on in the body; as, for example, in the bone marrow and possibly other organs. It is, however, difficult to reconcile our slight positive balance with Umber's marked negative balance, before operation.

The cases to which Pearce refers, as exhibiting a positive nitrogen balance, are one of congenital hemolytic icterus (8) and one of pernicious anemia (9). In neither instance was there more than a slight positive nitrogen balance before splenectomy and in the case of pernicious anemia, some time after the operation, there was no increased assimilation of nitrogen. Both cases were studied for short periods only. It may be concluded, therefore, that a markedly positive nitrogen balance has not as yet been observed in pernicious anemia.

The following cases of pernicious anemia were put on high diets. The food was made as appetizing as possible, the personal wishes of the patients were consulted and no attempt was made to maintain a definite proportion of proteins, fats or carbohydrates. It is notoriously difficult to administer large quantities of food to many cases of pernicious anemia. This problem was encountered only with H. M., Medical No. 37787. However, careful nursing and attention to a moderate degree of myocardial insufficiency finally won the day and this man consumed a fair amount of food, though never with the same relish as the other cases. It is not intended to convey the impression that it has been possible to force feeding in every patient. In fact, G. R. B., Medical No. 36704, after doing splendidly for some time following his discharge from the hospital, threw all precautions to the winds, stopped his hydrochloric acid, indulged in a great deal of alcohol, and finally returned for treatment. After one month's attempt, under ideal conditions, and with the patient's enthusiastic co-operation, it was found impossible to administer a high diet.

These patients were all kept under strict supervision in a small metabolism ward. They remained in bed, thus establishing their metabolic requirements at as low a level as possible. The only medication which they received was dilute hydrochloric acid. In one case transfusions were given. The food values were calculated according to Atwater and Bryant's tables. An actual analysis of a considerable number of samples showed that such calculations were accurate for the food materials used. The nitrogen of the urine and feces was determined by the Kjeldahl method.

The histories and results of observations in these cases are as follows:

G. R. B. Medical No. 36704. Male, white, aged 50.
Diagnosis: Pernicious anemia.
Admitted to The Johns Hopkins Hospital October 2, 1916.

The patient lived in Mississippi up to five years ago, and during that time had chills and fever every year. He complains of weakness and shortness of breath on exertion. He has had numbing and tingling in the legs occasionally, and has noted that his skin has been somewhat yellow.

On admission, he was well developed and nourished but extremely pale. The scleræ had a lemon yellow color. The area of precordial dulness measured 4 x 12 cm. There was a blowing systolic murmur over the entire precordium. The liver was felt one finger's breadth below the costal margin; the spleen was not felt. Otherwise, the physical examination was negative.

On October 3, the red blood cells were 1,216,000, the hemoglobin 28 per cent., the white blood cells 5200, and the differential count was as follows: Polymorphonuclear neutrophiles 64 per cent, lymphocytes 16 per cent, large mononuclear cells 7 per cent, eosinophiles 3 per cent, basophiles 1 per cent, myelocytes 3 per cent, transitionals 3 per cent, and unclassified cells 3 per cent. The blood smear showed a moderate variation in size and shape of the red blood cells, with a tendency towards the large type of red blood cell. The red cells were deeply and diffusely stained and no nucleated red cells were seen; there was a slight degree of basophilia, but no granular degeneration. The blood platelets appeared to be decreased.

On October 15, thirteen days after admission, after two transfusions had been given, and the red cells had increased to almost 2,000,000, the forced feeding was begun. The further course of events may be followed in Table 1. During this period he received two additional transfusions, as indicated on the chart, and was taking 20 to 40 minims of dilute hydrochloric acid after meals. No other medication, except an occasional cathartic, was given. The patient was kept in bed while these observations were made.

H. M. Medical No. 37787. Male, white, aged 60.
Diagnosis: Pernicious anemia.
Admitted to The Johns Hopkins Hospital April 14, 1917.

In March, 1915, following an "attack of grippe," he was short of breath and weak. In the spring of 1916, his skin began to burn, itch and tingle. He was very hypersensitive to odors, but nothing abnormal could be found in his nose by specialists. His eyes became weaker and black dots impaired his vision. This condition became worse until at present he can scarcely read more than 15 minutes at a time. In April, 1916, shortness of breath, paleness, jaundice and weakness became so marked that he went to the Bermuda Islands to recover, but obtained no relief. In the winter of 1916-17, he was so weak and short of breath that he could scarcely walk. He went to Florida and his symptoms cleared up to a remarkable degree. Later, he again relapsed and he came to the hospital for treatment. His appetite is very poor and his bowels are constipated.

The patient was extremely pale. There was marked dyspnea even on slight exertion. The skin and scleræ had a lemon yellow color. He was well nourished. There were numerous fresh and old hemorrhages scattered throughout both retinæ. The area of precordial dulness extended 3 cm. to the right and 12 to the left. At the apex there was a soft blowing systolic murmur. The second pulmonic sound was louder than the aortic second. The pulse was regular in force and frequency. The rate varied from 80 to 95. The blood pressure was 110 systolic and 60 diastolic. The liver edge was at the costal margin; the spleen was felt one finger's breadth below the costal margin; it appeared to be soft. On April 19 the red blood cells were 1,000,000, the hemoglobin 25 per cent, and the white blood cells 4600. On May 5 the differential count showed 55.6 per cent polymorphonuclear cells, 35.2 per cent lymphocytes, 5.2 per cent large mononuclear cells, 2 per cent transitionals, 1.6 per cent eosinophiles, and 0.4 per cent basophiles. The blood smear on April 18 showed great variation in the size and shape of the red cells; there were many microcytes and macrocytes; the red blood cells were of a dark color and diffusely stained; there was a moderate number of normoblasts and megaloblasts; there was

TABLE 1.—RESULTS OF FORCED FEEDING IN A CASE OF PERNICIOUS ANEMIA (G. R. B., MED. NO. 36704)

Date	Food					Nitrogen per day, gm.					Blood		Transfusion citrated, blood, c.c.	Weight, kg.
	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Total calories	Calories per kilo per day	Urine	Feces	Total output	Intake	Balance	Red blood cells per c. mm.	Hemoglobin per cent		
10–15–16	89.5	128.4	289.9	2750	39.1	10.69	3.18	13.87	14.3	+ .43	.....	..	...	70.3
10–16–16	106.1	159.6	276.7	3054	43.3	8.45	3.00*	11.45	16.9	+5.45	2,016,000	36	...	70.4
10–17–16	103.2	184.1	326.6	3474	49.4	8.53	3.00*	11.53	16.5	+4.97	.....	..	...	70.2
10–18–16	114.5	133.5	353.2	3159	44.8	9.89	3.00*	12.89	18.3	+5.41	.....	..	...	70.4
10–19–16	95.9	183.5	324.4	3430	48.5	10.92	2.13	13.05	15.3	+2.25	.....	..	...	70.6
10–20–16	100.1	139.9	306.3	2967	42.1	7.17	2.13	9.30	16.0	+6.70	1,716,000	36	...	70.4
10–21–16	112.9	201.6	301.1	3572	50.7	12.43	4.24	16.67	18.1	+1.43	.....	..	...	70.4
10–22–16	118.0	177.3	411.0	3818	54.0	9.27	3.79	13.06	18.9	+5.84	.....	..	...	70.6
10–23–16	117.8	172.8	391.0	3693	51.6	13.44	3.02	16.46	18.8	+2.34	.....	..	...	71.3
10–24–16	99.1	132.3	273.2	2757	38.9	13.99	3.02	17.01	15.9	−1.11	1,848,000	36	500	70.7
10–25–16	69.4	86.9	174.0	1806	25.4	7.55	1.61	9.16	11.1	+1.94	2,248,000	39	...	70.9
10–26–16	116.8	161.8	377.1	3130	50.7	12.80	1.61	14.41	18.7	+4.27	.....	..	...	69.6
10–27–16	116.3	202.0	371.8	3880	54.9	12.15	1.61	13.76	18.6	+4.84	.....	..	...	70.6
10–28–16	106.1	200.3	430.3	4063	57.6	10.43	2.98	13.41	17.0	+3.59	.....	..	...	70.5
10–29–16	100.8	160.1	505.3	3974	56.2	9.27	2.98	12.25	16.1	+3.85	.....	..	...	70.7
10–30–16	117.2	160.3	498.3	4014	56.2	10.35	5.22	15.57	18.8	+3.23	.....	..	...	71.3
10–31–16	77.7	127.1	402.9	3152	43.9	8.95	2.17	11.12	12.4	+1.28	2,328,000	39	500	71.7
11– 1–16	85.2	149.6	295.9	2954	41.1	11.34	2.17	13.51	13.6	+ .09	2,368,000	40	...	71.5
11– 2–16	123.8	165.2	500.0	4094	57.5	11.99	2.17	14.16	19.8	+5.64	.....	..	...	71.1
11– 3–16	129.5	180.0	518.8	4332	61.0	9.14	3.45	12.59	20.7	+8.11	.....	..	...	71.0
11– 4–16	97.6	183.9	500.0	4160	58.3	11.93	3.45	15.38	15.6	+ .22	.....	..	...	71.3
11– 5–16	90.7	121.2	442.9	3315	46.2	9.59	3.45	13.04	14.5	+1.46	.....	..	...	71.7
11– 6–16	111.2	157.5	272.4	3038	42.4	13.57	3.45	17.02	17.8	+ .78	3,224,000	45	...	71.5
11– 7–16	93.8	150.1	501.6	3837	54.0	11.03	3.40	14.43	14.9	+ .47	.....	..	...	71.0
11– 8–16	122.2	164.9	507.8	4117	57.8	10.52	3.40	13.92	19.6	+5.68	.....	..	...	71.2
11– 9–16	103.7	160.4	544.5	4149	57.6	9.90	3.40	13.30	16.6	+3.30	.....	..	...	71.9
11–10–16	124.0	220.9	504.1	4630	63.5	6.82	3.45	10.27	19.8	+9.53	.....	..	...	72.8
11–11–16	99.4	139.1	469.2	3625	49.8	10.16	3.45	13.61	15.9	+2.29	2,760,000	48	...	72.8

*The nitrogen content of the feces was estimated on these days ; the remaining figures represent actual determinations.

TABLE 2.—RESULTS OF FORCED FEEDING IN A CASE OF PERNICIOUS ANEMIA (H. M., MED. NO. 37787)

Date	Food						Nitrogen per day, gm.					Blood		Weight, kg.
	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Alcohol, gm.	Total calories	Calories per kilo per day	Urine	Feces	Total output	Intake	Balance	Red blood cells per c. mm.	Hemoglobin, per cent	
4–18–17	52.2	84.0	193.8	....	1790	26.6	7.74	2.00	9.74	8.35	— 1.39	.....	..	67.2
4–19–17	50.9	87.0	144.3	....	1610	23.8	6.11	2.00	8.11	8.14	+ 0.03	1,000,000	25	67.6
4–20–17	79.3	173.6	258.9	13.9	3097	45.6	5.28	2.00	7.28	12.68	+ 5.40	.....	..	67.8
4–21–17	68.1	137.8	336.8	18.5	3072	44.7	7.06	2.00	9.06	10.89	+ 1.83	1,476,000	28	68.7
4–22–17	83.0	177.7	287.6	27.6	3365	48.4	5.44	1.80	7.24	13.28	+ 6.04	.....	..	69.5
4–23–17	101.5	225.6	267.2	13.9	3706	53.4	Lost	1.80	1.80+	16.24	+14.44	.....	..	69.4
4–24–17	88.8	216.8	339.0	13.9	3867	54.9	8.03	1.80	9.83	14.20	+ 4.40	1,504,000	24	70.3
4–25–17	119.3	224.7	321.8	13.9	3995	56.6	7.39	1.80	9.19	19.07	+ 9.88	.....	..	70.6
4–26–17	111.3	244.4	355.8	13.9	4285	60.7	8.20	1.80	10.00	17.80	+ 7.80	.....	..	70.5
4–27–17	113.3	251.5	362.3	13.9	4386	61.8	6.57	1.80	8.37	18.12	+ 9.75	2,356,000	30	70.9
4–28–17	119.3	245.6	334.1	13.9	4240	59.3	7.44	1.72	9.16	19.08	+ 8.92	.....	..	71.5
4–29–17	122.8	236.3	368.1	13.9	4307	60.6	8.58	1.72	10.30	19.64	+ 9.34	2,308,000	34	71.0
4–30–17	130.9	234.1	372.4	13.9	4338	61.4	8.00	1.72	9.72	20.94	+11.22	.....	..	70.6
5– 1–17	115.4	253.5	357.0	13.9	4392	62.3	9.04	1.72	10.76	18.46	+ 7.70	2,224,000	42	70.4
5– 2–17	137.3	247.6	309.5	13.9	4232	60.4	9.41	1.72	11.13	21.96	+10.83	.....	..	70.6
5– 3–17	123.0	226.4	355.5	13.9	4165	59.3	10.98	2.06	13.04	19.68	+ 6.64	2,670,000	46	70.2
5– 4–17	134.0	256.9	317.7	13.9	4338	61.4	10.98	2.06	13.04	21.44	+ 8.40	.....	..	70.5
5– 5–17	140.9	250.8	382.1	13.9	4574	64.7	11.13	2.06	13.19	22.54	+ 9.35	3,068,000	46	70.6
5– 6–17	123.5	257.9	381.9	13.9	4567	64.4	9.65	2.06	11.71	19.76	+ 8.05	.....	..	70.8
5– 7–17	143.0	257.9	348.8	13.9	4511	63.6	10.44	2.06	12.50	22.88	+10.38	2,954,000	48	70.9
5– 8–17	153.5	263.1	404.9	13.9	4833	68.2	10.67	2.06	12.73	24.56	+11.83	.....	..	70.8
5– 9–17	146.3	261.6	361.6	13.9	4613	64.9	13.25	2.13	15.38	23.40	+ 6.02	2,976,000	52	71.0
5–10–17	157.4	270.3	382.9	....	4729	66.6	13.17	2.13	15.30	25.18	+ 9.88	.....	..	70.9
5–11–17	151.8	261.4	421.9	....	4783	66.7	13.32	2.13	15.45	24.28	+ 8.83	.....	..	71.7
5–12–17	128.3	245.1	391.5	....	4410	61.6	13.07	2.13	15.20	20.52	+ 5.32	3,240,000	54	71.5
5–13–17	146.7	249.2	366.4	....	4421	61.6	13.46	2.07	15.53	23.47	+ 7.94	.....	..	71.7
5–14–17	152.6	256.7	421.8	....	4742	66.0	14.95	2.07	17.02	24.41	+ 7.39	3,016,000	55	71.8
5–15–17	156.9	258.2	353.9	....	4495	62.2	15.20	2.07	17.27	25.10	+ 7.83	.....	..	72.1
5–16–17	168.7	292.3	337.1	....	4792	66.3	16.56	2.07	18.63	26.99	+ 8.36	3,376,000	57	72.2
5–17–17	151.2	285.6	376.0	....	4818	67.0	13.16	2.07	15.23	24.19	+ 8.96	.....	..	71.8
5–18–17	153.6	266.7	426.3	....	4858	66.8	15.62	2.07	17.69	24.57	+ 6.88	3,728,000	60	72.7
5–19–17	166.0	263.3	373.1	....	4660	64.1	14.47	2.07	16.54	25.56	+10.02	.....	..	72.7

granular degeneration and basophilia, and the blood platelets were diminished.

The patient's symptoms were evidently caused by anemia and insufficient heart action. The only medication which he received was infusion of digitalis and dilute hydrochloric acid. With these aids his dyspnea was diminished and his appetite increased. The diet, the red blood cell counts and the percentage of hemoglobin may be followed in Table 2. His diet was forced as much as possible from April 18 until May 20. During this period he remained in bed. On May 20 he felt so well, the dyspnea, weakness and dimness of vision having disappeared completely, that he insisted on leaving the hospital.

W. B. Medical No. 36933. Male, white, aged 63.

Diagnosis: Pernicious anemia; lobar pneumonia.

Admitted to The Johns Hopkins Hospital September 21, 1916.

The patient was well until two days prior to his admission to the hospital. At this time he had a chill and complained of pain in the back. He was admitted to the hospital in an almost stuporous condition and was difficult to arouse. He had been working as sexton in a church until he was taken sick and had been doing fairly hard work.

The patient had the signs and symptoms of a lobar pneumonia in the right lower lobe. These cleared up shortly, so that six days after admission the temperature was normal and all traces of the acute disease had disappeared. The physical examination exclusive of the signs that could be referred to the pneumonia showed that the patient was fairly nourished but was very pale. There was slight edema above the ankles. The scleræ had a lemon tint; there were numerous small hemorrhagic spots upon the retinæ. Over the whole precordium there was a blowing systolic murmur which was not transmitted to the left beyond the apex region. The spleen was not felt; the liver was two fingers' breadth below the costal margin. Otherwise the physical examination was negative. On September 21, the red blood cells were 656,000, the hemoglobin was 15 per cent, and the white blood cells 3500. The differential count showed that the polymorphonuclear neutrophiles were 60 per cent, the lymphocytes 34.5 per cent, the large mononuclears 3.5 per cent, the transitionals 1.5 per cent, and the basophiles 0.5 per cent. The cells varied very much in size and shape; very many were distinctly larger than normal. There was basophilic and granular degeneration. A few megaloblasts and normoblasts were present.

The patient was transfused twice and given two courses of sodium cacodylate. On November 17, his red blood cells had risen to 3,500,000, and his hemoglobin to 70 per cent. This was almost exactly two months after his admission to the hospital. At that time, forced feeding was begun, the results of which are given in Table 3. During the period of high diet, he was given 20 minims of dilute hydrochloric acid after meals, but no other medication, and was kept in bed.

S. F. Medical History No. 37840. Male, white, aged 38.

Diagnosis: Chronic myeloid leukemia, secondary anemia.

Admitted to The Johns Hopkins Hospital December 17, 1916.

Seven years ago the patient first noticed that his abdomen was increasing in size. He was treated in the University Hospital of Baltimore one year later with X-rays, the diagnosis being splenomyelogenous leukemia. As the result of this therapy the spleen became very much smaller. Two years later he began to take arsenic, which he continued up to one year ago. The tumor in the abdomen has progressively increased in size; there have been frequent nosebleeds. The patient bleeds easily and a small injury will cause a bruise. On November 19, 1916, the patient went to Dr. Kelly's sanatorium, where he took three treatments of radium about 8 to 10 days apart. Under this therapy his spleen shrank markedly and he felt stronger than before. After an interval of three weeks, his gums became swollen and began to bleed. Ten days ago, epistaxis began and he bled for four days and four nights, losing a great deal of blood. At about the same time, small hemorrhages appeared in the skin. These would soon disappear and be replaced by a new crop.

The patient was well nourished. There was no dyspnea. He was constantly expectorating blood and blood was oozing from the nostrils and the gums. There were numerous hemorrhages in the skin. These were especially marked in the lower extremities. The largest ones were in the back, being 10 x 5 cm. The skin and scleræ had a peculiar orange tint. The heart and lungs showed nothing of note. The liver edge was felt at the costal margin; the spleen was remarkably enlarged, extending to about the level of the crest of the ilium below and almost to the median line on the right. The red blood cells were 3,120,000; the white blood cells 4600; the hemoglobin 30 per cent. The differential count showed polymorphonuclear cells 74.8 per cent, small mononuclear cells 16 per cent, large mononuclear cells 6.8 per cent, transitional cells 0.4 per cent, myelocytes 0.8 per cent, eosinophiles 0.4 per cent, and basophiles 0.8 per cent. Before radiation the blood count had been: Red blood cells 2,984,000; white blood cells 160,000; hemoglobin 52 per cent; and the differential count: Polymorphonuclear neutrophiles 20.7 per cent, small mononuclear cells 10.0 per cent, large mononuclear cells 2.3 per cent, transitional cells 1.6 per cent, myelocytes 5.5 per cent, basophiles 3.3 per cent, and eosinophiles 3.6 per cent.

From December 17 to March 2 numerous transfusions were given, and arsenic therapy was employed. There was no improvement; the bleeding from the nasopharynx, which continued during this period, finally resulting in a very severe secondary anemia. The blood platelet count was very low; the blood clot did not contract but was typical of a clot deficient in blood platelets. A marked leucopenia accompanied this secondary anemia. There were several retinal hemorrhages and marked bleeding from the gums. Hemorrhages into skin were present to only a very slight degree. On March 2 the red blood cell count was 912,000, the hemoglobin 20 per cent and the white blood cells 1350. On this date forced feeding was begun, the hemorrhages ceased, and the further course of the patient can be followed in Table 4.

It is very evident from the study of the figures as given in Tables 1, 2 and 3, that there was no difficulty encountered at any time during the observation in bringing about an extensive assimilation of nitrogen. In the case of G. R. B., Table 1, the only patient in whom transfusions were employed, it may be noted that following each of the transfusions there was a lowered nitrogen balance. This was only to be expected, inasmuch as the nitrogen contained in the transfused blood was not included in the intake. This result would indicate that much of the protein material contained in the blood introduced intravenously was lost in the urine. The positive nitrogen balance diminished considerably a few days after the second transfusion. The patient did not consume as much food on some of these days, and it is very difficult to ascertain the exact reasons for these fluctuations. The other two cases, who were not transfused (Tables 2 and 3) certainly exhibited a much steadier positive nitrogen balance. The amount of nitrogen and the caloric value of the diet may possibly be most readily appreciated from the summary given in Table 5. One of these patients retained 3.4 gms. of nitrogen a day for 28 days, another, 3.4 gms. a day for 32, and the third 6.8 gms. a day for 36 days. These are very large positive balances, and there can be no doubt that cases of pernicious anemia can assimilate nitrogen readily if put upon forced diets.

TABLE 3.—RESULTS OF FORCED FEEDING IN A CASE OF PERNICIOUS ANEMIA (W. B., MED. NO. 36933)

Date	Food					Nitrogen per day, gm.					Blood		Weight, kg.
	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Total calories	Calories per kilo per day	Urine	Feces	Total output	Intake	Balance	Red blood cells per c. mm.	Hemoglobin per cent	
11–16–16	79.9	125.0	230.1	2434	48.9	10.49	0.43	10.92	12.78	+ 1.86	.....	..	49.7
11–17–16	80.2	125.2	229.0	2432	49.6	10.06	0.43	10.49	12.83	+ 2.34	3,500,000	70	49.0
11–18–16	79.9	125.7	230.1	2440	49.7	8.21	0.42	8.63	12.78	+ 4.15	.....	..	49.0
11–19–16	80.2	124.0	230.5	2427	49.8	11.32	1.58	12.90	12.83	— 0.07	3,000,000	68	48.7
11–20–16	79.0	126.8	400.2	3144	63.6	10.56	1.58	12.14	12.64	+ 0.50	.....	..	49.4
11–21–16	80.2	123.9	400.2	3122	62.4	8.93	1.58	10.51	12.83	+ 2.32	.....	..	50.0
11–22–16	80.2	126.5	400.1	3145	62.2	8.57	1.58	10.15	12.83	+ 2.68	.....	..	50.5
11–23–16	81.4	124.9	399.9	3136	61.6	7.84	1.58	9.42	13.02	+ 3.60	4,000,000	74	50.9
11–24–16	81.2	125.1	401.7	3143	61.7	7.76	1.58	9.34	12.99	+ 3.65	.....	..	50.9
11–25–16	80.2	125.2	400.6	3135	61.4	5.60	1.58	7.18	12.83	+ 5.65	.....	..	51.0
11–26–16	80.5	125.7	401.8	3146	61.2	5.94	1.82	7.76	12.88	+ 5.12	.....	..	51.4
11–27–16	80.2	125.0	402.1	3141	60.7	6.03	1.82	7.85	12.83	+ 4.98	4,176,000	70	51.7
11–28–16	80.5	125.5	401.1	3142	60.3	5.06	1.82	6.88	12.88	+ 6.00	.....	..	52.1
11–29–16	80.6	124.9	400.7	3135	59.9	4.84	1.82	6.66	12.89	+ 6.23	.....	..	52.3
11–30–16	80.2	125.0	402.1	3141	59.6	4.08	2.51	6.59	12.83	+ 6.24	.....	..	52.7
12– 1–16	79.8	125.1	400.0	3130	59.3	3.74	2.51	6.25	12.76	+ 6.51	.....	..	52.7
12– 2–16	80.4	125.8	400.9	3144	59.2	2.98	2.38	5.36	12.86	+ 7.50	.....	..	53.1
12– 3–16	80.2	125.2	400.6	3135	58.4	4.50	2.37	6.87	12.83	+ 5.96	.....	..	53.6
12– 4–16	80.6	125.0	400.8	3136	58.5	4.51	2.37	6.88	12.89	+ 6.01	4,563,000	73	53.6
12– 5–16	80.2	124.9	401.2	3136	58.1	5.10	2.37	7.47	12.83	+ 5.36	.....	..	53.9
12– 6–16	89.2	103.3	251.5	2358	43.8	5.22	2.61	7.83	14.27	+ 6.44	.....	..	53.8
12– 7–16	80.1	124.9	400.3	3131	59.2	7.08	2.61	9.69	12.81	+ 3.12	.....	..	52.8
12– 8–16	80.3	125.6	400.6	3139	58.4	6.04	2.61	8.65	12.84	+ 4.19	4,600,000	68	53.7
12– 9–16	80.1	125.4	400.8	3137	57.7	4.47	2.61	7.08	12.81	+ 5.73	.....	..	54.3
12–10–16	80.2	125.2	400.6	3135	58.2	5.28	2.80	8.08	12.83	+ 4.75	.....	..	53.8
12–11–16	80.7	125.5	400.7	3141	57.4	5.54	2.80	8.34	12.91	+ 4.57	.....	..	54.7
12–12–16	80.2	125.6	400.1	3137	57.2	5.05	2.80	7.85	12.83	+ 4.98	4,160,000	73	54.8
12–13–16	91.3	95.4	274.1	2385	43.3	6.00	2.80	8.80	14.60	+ 5.80	.....	..	55.0
12–14–16	80.6	125.0	400.2	3134	57.6	4.94	2.80	7.74	12.89	+ 5.15	.....	..	54.4
12–15–16	80.0	125.4	400.4	3136	57.0	6.21	2.80	9.01	12.80	+ 3.79	.....	..	55.0
12–16–16	145.9	135.1	273.4	2975	54.0	7.19	2.80	9.99	23.34	+13.35	.....	..	55.0
12–17–16	80.0	125.8	400.0	3138	57.7	9.00	2.80	11.80	12.80	+ 1.00	.....	..	54.3
12–18–16	80.3	125.5	400.4	3138	57.2	7.13	3.03	10.16	12.84	+ 2.68	.....	..	54.8
12–19–16	80.0	125.5	400.0	3135	56.5	6.93	3.03	9.96	12.80	+ 2.84	.....	..	55.4
12–20–16	80.1	124.9	400.3	3131	56.3	6.49	3.03	9.52	12.81	+ 3.29	.....	..	55.6
12–21–16	80.0	125.8	400.0	3138	55.9	5.43	3.03	8.46	12.80	+ 4.34	4,040,000	77	56.1

TABLE 4.—RESULTS OF FORCED FEEDING IN (S. F., MEDICAL NO. 37840) A CASE OF CHRONIC MYELOGENOUS LEUKEMIA, COMPLICATED BY SECONDARY ANEMIA, BROUGHT ABOUT BY HEMORRHAGES FOLLOWING RADIUM THERAPY

Date	Food					Nitrogen per day, gm.					Blood		Weight kg.
	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Total calories	Calories per kilo per day	Urine	Feces	Total output	Intake	Balance	Red blood cells per c. mm.	Hemoglobin per cent	
3– 3–17	118.1	165.8	372.8	3554	59.6	.....	3.23	.....	18.89	.....	912,000	20	59.6
3– 4–17	120.5	159.7	319.4	3289	55.1	12.17	3.23	15.40	19.28	+ 3.88	1,152,000	22	....
3– 5–17	134.9	176.1	375.2	3729	62.5	13.12	3.23	16.35	21.58	+ 5.23	1,536,000	24	....
3– 6–17	114.6	160.6	399.1	3599	60.3	14.10	3.23	17.33	18.33	+ 1.00	.....	..	....
3– 7–17	123.1	159.1	389.1	3580	60.0	10.29	3.23	13.52	19.69	+ 6.17	1,392,000	25	....
3– 8–17	125.2	155.3	402.4	3607	60.5	13.32	3.23	16.55	20.03	+ 3.48	1,172,000	23	....
3– 9–17	135.2	184.2	414.0	3964	59.9	10.11	1.97	12.08	21.63	+ 9.55	1,444,000	25	66.1
3–10–17	157.5	174.9	411.6	3961	59.9	13.79	1.97	15.76	25.20	+ 9.44	1,842,000	28	....
3–11–17	85.7	96.4	298.2	2471	37.3	11.10	1.97	13.07	13.71	+ 0.64	1,572,000	28	....
3–12–17	137.4	181.3	427.6	4002	....	9.80	1.97	11.77	21.98	+10.21	1,664,000	30	....
3–13–17	143.5	176.6	431.7	4001	62.7	11.90	1.97	13.87	22.96	+ 9.09	1,584,000	31	63.7
3–14–17	140.2	174.0	440.9	4001	61.9	13.62	2.46	16.08	22.43	+ 6.35	1,688,000	30	64.6
3–15–17	139.9	189.0	416.6	4002	61.9	9.73	2.46	12.19	20.94	+ 8.75	1,840,000	34	64.6
3–16–17	125.5	172.5	459.7	4004	62.0	10.50	2.46	12.96	20.08	+ 7.12	.....	..	64.5
3–17–17	156.7	208.0	469.8	4503	69.3	4.59	2.46	7.05	25.07	+18.02	1,856,000	..	64.9
3–18–17	151.7	189.8	515.5	4501	68.6	12.27	2.46	14.73	24.27	+ 9.54	1,780,000	..	65.6
3–19–17	145.0	195.0	510.6	4502	68.6	11.28	2.46	13.74	23.20	+ 9.46	.....	..	65.6
3–20–17	150.8	194.8	505.0	4501	68.4	11.94	2.25	14.19	24.12	+ 9.93	1,984,000	..	65.8
3–21–17	163.0	206.8	465.6	4500	68.2	12.64	2.25	14.89	26.08	+11.19	1,904,000	..	66.0
3–22–17	162.3	194.0	514.4	4579	69.0	12.47	2.25	14.72	25.96	+11.24	2,128,000	37	66.3
3–23–17	154.3	212.7	461.3	4502	67.5	11.38	2.25	13.63	24.68	+11.05	.....	..	66.6
3–24–17	162.8	214.8	447.6	4500	67.3	12.24	2.25	14.49	26.04	+11.55	1,984,000	38	66.8
3–25–17	147.1	176.9	549.7	4502	67.2	13.20	2.25	15.45	23.53	+ 8.08	2,204,000	38	66.9
3–26–17	165.9	215.4	446.7	4515	67.3	11.71	2.25	13.96	26.54	+12.58	.....	..	67.0
3–27–17	162.9	211.0	456.5	4502	66.9	13.75	3.17	16.92	26.06	+ 9.14	2,400,000	40	67.2
3–28–17	160.9	201.1	480.8	4501	66.8	14.56	3.17	17.73	25.74	+ 8.01	2,368,000	45	67.3
3–29–17	150.6	217.8	484.4	4629	68.1	14.44	3.17	17.61	24.09	+ 6.48	2,468,000	48	67.9
3–30–17	157.6	208.8	465.8	4498	66.3	12.96	3.17	16.13	25.21	+ 9.08	2,356,000	48	67.8
3–31–17	175.6	179.4	515.5	4502	66.0	15.31	1.59	16.90	28.09	+11.19	2,516,000	51	68.2
4– 1–17	161.5	201.9	478.4	4501	65.8	15.48	1.59	17.07	25.84	+ 8.77	2,892,000	52	68.4
4– 2–17	177.3	180.4	518.0	4528	66.1	13.95	1.59	15.54	28.36	+12.82	.....	..	68.6
4– 3–17	90.8	100.8	264.8	2395	34.6	12.13	1.59	13.72	14.52	+ 0.80	2,788,000	55	69.1
4– 4–17	149.0	203.9	484.3	4493	66.2	12.88	1.59	14.47	23.84	+ 9.37	3,056,000	55	67.8

It is extremely hazardous to draw conclusions from such a small number of cases in regard to the effect of the diet on the hemoglobin and red cells. The tendency to remissions which cases of pernicious anemia constantly manifest makes it impossible to say definitely what rôle the diet played in influencing the blood picture. In two of the cases the improvement was not very striking; the hemoglobin rose from 36 to 48 per cent in G. R. B. in 28 days (Tables 1 and 5); during that time the patient received two transfusions; in W. B. the hemoglobin and red blood cells were only very slightly increased at the end of 36 days (Tables 3 and 5); in H. M., on the other hand, there was a very marked improvement, the hemoglobin rising from 25 to 60 per cent in 32 days and the red blood cells increasing correspondingly (Tables 2 and 5).

There is no doubt that the nitrogen in these cases is retained. The question as to what use the body makes of it is another matter. Is it permanently assimilated or would it be excreted if the observations were continued long enough? Is it useful to the body in regenerating blood cells? What proportions of carbohydrate fat and protein will yield the best results? These and a host of other queries are naturally suggested by the cases reported above and it is obvious that the answers must be brought by more extensive experiments.

A control case of secondary anemia (Tables 4 and 5) was treated in the same manner as the patients with pernicious anemia, with the exception that no hydrochloric acid was given. This individual received a higher caloric diet than the other cases. His desire for food was enormous and even with an intake of 68.9 calories per kilo, he claimed that he could easily manage a little more. The nitrogen assimilation in this patient was decidedly higher than in those with pernicious anemia. This may have been accidental, but it suggests that the element of protein destruction does play a considerable rôle in pernicious anemia. The gain in hemoglobin and red blood cells was almost identical with that seen in H. M. (Tables 2 and 5).

Conclusions.—By means of a forced diet a positive nitrogen balance may be readily obtained in pernicious anemia. Of the three cases observed, there was an improvement in the blood picture in each instance. The latter result must be regarded as suggestive only, inasmuch as too few patients have been studied to warrant a definite general conclusion.

Acknowledgment is due to Miss Susie McFarlane for organizing the Metabolism Ward in which these patients were studied, and for carrying out these difficult feeding experiments in a most efficient manner.

TABLE 5.—SUMMARY OF RESULTS (TABLES 1, 2, 3 AND 4) OF FORCED FEEDING IN THREE CASES OF PERNICIOUS AND ONE OF SECONDARY ANEMIA

Patient	Period, days	Food per day					Nitrogen per day, gm.			Hemoglobin during period of observation.		Red blood cells, during period of observation	
		Protein, gm.	Fat, gm.	Carbohydrate, gm.	Total calories	Calories per kilo per day	Intake	Output (Urine and Feces)	Balance	First	Last	First	Last
G. R. B.,* Pernicious Anemia.	28	105	161	395	3547	50.5	16.8*	13.4	+3.4	36	48*	2,016,000	2,760,000*
H. M., Pernicious Anemia.	32	125	234	344	4099	61.0	20.0	16.6	+3.4	25	60	1,000,000	3,728,000
W. B., Pernicious Anemia.	36	83	124	371	3015	60.7	13.3	6.5	+6.8	70	77	3,500,000	4,040,000
S. F., Secondary Anemia.	33	144	183	442	4105	68.9	23.0	14.3	+8.7	20	55	912,000	3,056,000

*This patient received two transfusions during the period of observation. The nitrogen contained in the transfused blood is not included in the intake; therefore, the nitrogen balance is more favorable in this case than appears in the table; the increase in the Hb. and the R. B. C. must be considered to be due to the transfusions as well as to forced diet.

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THE CLINICAL SIGNIFICANCE OF THE IRREGULAR DISTRIBUTION OF VARIOUS CELLS AND PARASITES IN THE BLOOD STREAM AND THE PRODUCTION OF ABORTIVE LEUKÆMIC CHANGES AND OF SPLENOMEGALY IN THE MACACUS RHESUS

By ANDREW WATSON SELLARDS and WALTER ALBERT BAETJER

OUTLINE

I. Predominance of Biological Rather than Mechanical Laws in the Circulation of Various Substances in the Blood Stream.
   1. Consideration of normal substances under normal and under pathologic conditions.
   2. Behavior of foreign material.
      a. Disappearance of foreign material from the peripheral circulation shortly after injection.
      b. Temporary disappearance of leucocytes from the circulation after the injection of foreign substances.
      c. Irregular distribution of parasites in spontaneous infections.

II. Interpretation of Leucocyte Counts.
   1. Distinction between changes in absolute number and changes in distribution in the body.
      a. Occurrence of acute temporary leucocytosis.
      b. Occurrence of acute temporary leucopœnia.
   2. Factors governing the leucocyte count.
      a. Infecting organism.
      b. Location of infection in host.
      c. Severity and stage of infection.

III. Choice of Site of Infection for the Transmission of Infectious Diseases.
   1. Disadvantages of intravenous injection.
      a. Dilution of material.
      b. Deleterious action of blood serum and cells.
      c. Removal of microscopic particles by lungs and other organs.
      d. Danger of embolism.
   2. Advisability of concentrating the infecting agent in a susceptible area.

IV. Special Considerations in Regard to Leukæmia.
   1. Selection of spleen as site of injection.
   2. Susceptibility and resistance of spleen to infection.
   3. Mechanical advantages.
   4. Clinical advantages.
   5. Production of abortive leukæmic changes in *Macacus rhesus*.

PART I. GENERAL CONSIDERATIONS.

Of the many remarkable features connected with the blood and its circulation, considerable interest is associated with the conditions governing the distribution in the circulation of the normal elements of the blood under natural conditions and also of foreign elements upon introduction into the blood stream. Even a cursory examination of a few details is sufficient to disclose the fact that organized cells and probably substances in solution do not circulate according to mechanical laws, but that their distribution is governed by biological conditions. A simple illustration will make this more explicit. When a suspension of nucleated red corpuscles is injected intravenously into a rabbit, these cells disappear from the circulation within a few minutes instead of becoming equally distributed through the blood, as in a mechanical suspension *in vitro*. In this discussion, mechanical laws are contrasted with biological conditions, but without any intention of opening the question of the explanation that is involved. Thus, it is entirely conceivable that the biological conditions may rest, in their ultimate analysis, either upon physical conditions or upon vitalistic phenomena.

There is a considerable amount of data, extending over a long period in the literature, in regard to the distribution of normal and foreign substances in the blood stream; indeed, there are many observations coming often from unexpected sources which supply information on this subject. We have carried out a few simple experiments to confirm some of the essential phenomena which have been reported. The general clinical significance of these will be discussed briefly, but special attention will be given to the factors bearing upon the transmission of infectious diseases.

CIRCULATION OF THE NORMAL CONSTITUENTS OF THE BODY

Even under normal conditions, the cellular elements of the blood are not distributed in a purely mechanical way, but are subject to variation as the result of changes which are purely physiological in their nature. Examples of this are to be found in the fluctuations in the number of leucocytes in the peripheral blood, such as the leucocytosis of digestion, after cold baths, and after exercise. Here it is evident that the increase is due essentially not to the withdrawal of fluid from the blood, but to an increase in the number of white cells in the peripheral circulation. The red cell count is also subject to fluctuation. Lamson [1] has shown that there is a mechanism for regulating the red cell content of the circulating blood, that this mechanism is under nervous control and that it is the liver which supplies the body with preformed red cells to meet the acute demands.

There are many types of cells which are ordinarily retained completely in the bone marrow and other blood spaces of the body, but after a more or less severe stimulus these cells appear in the peripheral circulation. Thus it is a little difficult to understand why nucleated red cells are not normally abundant in the circulating blood or why a myelocythæmia develops only after a very considerable stimulus such as the severe infections of diphtheria.

CIRCULATION OF FOREIGN SUBSTANCES IN THE BLOOD

A series of interesting changes follows the injection of foreign material into the blood stream. Various substances * either in solution or in suspension, when injected intravenously produce in a few minutes a profound leucopœnia, the majority of the polymorphonuclear cells disappearing from the peripheral circulation and collecting in the blood vessels of the viscera, especially in the lungs and liver, and to a much smaller extent, in the spleen. Moreover, when material in suspension is injected, the foreign particles are also withdrawn promptly from the circulation and collected in the viscera, especially in the lungs, the liver, and to a less extent in the spleen. It is noteworthy that the leucocytes disappear simultaneously with the foreign material and collect in these same viscera. As a general rule, the leucocytes themselves are not destroyed, but after a comparatively short time—a few minutes to a few hours—they return, often in increased numbers, to the peripheral circulation.

This distribution of foreign suspensions was thoroughly studied by Werigo [2]; he found that bacteria and also chemically inert particles such as carmine are promptly removed from the circulating blood. The essentials of these observations have been confirmed by Ewing.[3] Bruce [4], in 1894, investigated the well known phenomenon of the more or less complete disappearance of the polymorphonuclear cells from the peripheral circulation after the intravenous injection of peptone; *e. g.*, 20 c. c. of a 10 per cent solution. It had been supposed that this sudden disappearance of the white cells was due to a cytolytic action of the peptone, but Bruce was able to show definitely that the leucocytes collected in the blood vessels of the viscera, principally in the lungs, but also in the spleen, and in smaller numbers in the liver. The number appearing in the other organs, however, was almost nil, though the work of some authors indicates that the bone marrow is of some importance.† This similarity in the effect of peptone and foreign suspensions upon the distribution of the leucocytes suggests at once the possibility that the peptone may be withdrawn from the circulation corresponding in its behavior to that of suspended particles. Indeed it would be very helpful if the behavior of the leucocytes following the injections of a solution could be used as a criterion to determine whether the foreign substance in solution was distributed equally throughout the circulation, or whether it became concentrated in the viscera in a manner analogous to the behavior of foreign cells.

Experiments with Bacteria and Red Blood Cells.—The possibilities of the full significance of these experiments and their bearing upon inoculation experiments in lower animals can be understood best by observing the course of events that follows the intravenous injection of bacteria. The following observations were made in the course of the immunization of a rabbit against a staphylococcus of very low virulence. Upon the third injection, the 24-hour growth from 10 agar slants was emulsified in 3 c. c. of salt solution and injected into a vein of the right ear. A blood smear was made immediately before injection. The time required for injection was about two minutes; when it was completed, a blood smear was made from the left ear immediately and at successive intervals of 5, 10, 20, 30, 40, and 60 minutes. The smear before injection showed an abundance of leucocytes in every field with 88 per cent of polymorphonuclear cells. The smears immediately after injection showed very few white cells. In the smear five minutes after injection the majority of the fields under a 1/12 oil immersion lens were free from white cells. The differential count of 100 cells showed 96 per cent of mononuclear forms. The smear 10 minutes after injection showed increasing numbers of white cells over the preceding one; this increase went on rapidly and a smear 30 minutes after the injection did not differ in its general appearance from the one just before injection. No counts were made of the total number of white cells. The red cells were apparently unaffected. The behavior of the bacteria is even more interesting. With this massive quantity one would expect that they could be seen in the smears. However, the smear made immediately after injection showed no bacteria, either free in the blood or in the few leucocytes that were present; but, in the smears in which the leucocytes were returning to the peripheral blood, staphylococci were frequently found in the polymorphonuclear leucocytes; some cells even contained too many bacteria to be counted readily.

It happened that this animal had already received immunizing doses of staphylococci; on repetition with a normal animal essentially the same features were obtained, though not as sharply; after considerable search only a few bacteria were seen in the leucocytes upon their return to the peripheral circulation. It was found, too, that such large doses often killed the animals suddenly during the course of the injection. Apparently no observations have been conducted to determine whether immunization or infection of an animal would definitely modify its behavior in comparison with that of a normal individual. Any difference in a normal and immune animal in regard to the effect of foreign injections upon the distribution of the leucocytes would be very interesting, inasmuch as it would furnish a reaction for immunity which would be independent of any examination for immune bodies. Bull [5] has recently studied very thoroughly the phenomena of agglutination *in vitro* and *in vivo*. In many instances avirulent organisms are agglutinated *in vivo* in animals whose sera possess no agglutinating action *in vitro*. In contrast to these non-virulent organisms, Bull has made the further very interesting observation that certain virulent organisms are not agglutinated *in vivo* by animals whose serum possesses no agglutinating power *in vitro*. In some

* The earliest studies began in 1872, observations being made upon the effect of such substances as curare, fibrin ferment, hæmoglobin, septic fluids, lymph cells, split proteins, chemicals such as uric acid and the urates, and inert substances such as carmine. For detailed references see Sherrington, Proc. Roy. Soc., Lond., 1894, LV, 195.

† Although there is some variation in the individual instances, yet the reports of the various authors indicate that the liver plays a distinctly more prominent part than the spleen in the retention of leucocytes and foreign substances, while the lungs play a more important part than the liver, presumably because material injected intravenously passes first through the lungs.

respects it would be difficult to distinguish agglutination *in vivo* from the phenomenon observed in normal animals of the concentration of foreign particles in the viscera.

Hopkins and Parker[6] have very recently noted that after intravenous injection streptococci are quickly withdrawn by the lungs, liver, spleen, and in small numbers by other tissues. These authors have contributed the following very significant observations. Some hours after injection streptococci, which cannot maintain themselves in the circulation of a normal animal, begin to appear in the blood stream. This occurs notwithstanding the fact that the inoculated animal has not lost its power of removing freshly injected organisms.

On injecting typhoid bacilli, an organism ordinarily giving rise to leucopœnia in man, we observed the same immediate results in rabbits as with staphylococci. Five agar slants of an old culture of *B. typhosus* were injected intravenously into a rabbit. The smears after injection showed an outspoken diminution in the number of white cells for a period of 20 minutes.

Nucleated red cells upon injection behaved in the same general manner as other foreign agents, though the changes were less sharp. A half-grown rabbit was injected intravenously with 2 c. c. of a 50 per cent suspension of chicken corpuscles which had been washed twice with normal saline after collecting the blood in 1.5 per cent sodium citrate. The nucleated red cells could be seen in the blood smears in moderate numbers for several minutes after the injection. No phagocytosis was seen at any time. The leucocytes of the rabbit also diminished definitely. Counts were made at various intervals of the number of the red and white cells and the number of nucleated red cells with the following results:

TABLE I.—SHOWING THE RED AND WHITE COUNTS AND THE NUMBER OF NUCLEATED REDS AFTER INTRAVENOUS INJECTION OF A RABBIT WITH CHICKEN CORPUSCLES.

Time intervals	Red count	Leucocyte count	Nucleated red count of injected hen corpuscles
.....	4,500,000	5,500	.....
30 min.*	4,800,000	6,000	.....
3 min.	.....	600	42,000
7 min.	4,800,000	1,600	38,000
18 min.	5,100,000	2,900	12,000
42 min.	5,400,000	3,100	4,500
1½ hrs.	5,600,000	3,200	50
2½ hrs.	5,600,000	3,800	0
3½ hrs.	6,000,000	4,400	0
5½ hrs.	5,000,000	5,200	0

*Injection: 2 c. c. of washed chicken corpuscles.

The injection of mammalian (human) red cells, however, into a rabbit did not produce a leucopœnia. Certainly, therefore, with the injection of red cells from the same species, as in the blood transfusions, one would not expect any immediate and pronounced leucopœnia.

It has been shown by Goldscheider and Jacob[7] that the subcutaneous injection of an emulsion of certain organs such as the spleen and also the thymus and bone marrow, produces an acute, transient, leucopœnia. We also found that the intraperitoneal injection of pigeon corpuscles in a rabbit produced a definite, though less extreme, leucopœnia; however, this did not reach its most extreme grade till 20 minutes after the injection, and the white cell count did not return to normal till an hour had elapsed.

THE INFECTIOUS DISEASES

In considering the inoculation of diseases into animals, considerable interest centers in the natural distribution of parasites in certain spontaneous infections. There is abundant evidence that when the blood stream is infected, the micro-organisms are not distributed equally throughout the blood. Thus, in typhoid fever, it is very probable that the concentration of bacteria is greater in the spleen than in the peripheral blood and that they persist in the spleen after the circulating blood has become sterile. In connection with the comparative freedom of the extremities from rose spots in typhoid fever, it is interesting to note the apparent difficulty of reaching the peripheral parts of the body by injections into the blood stream. The malarial fevers furnish an excellent illustration of the irregular distribution of micro-organisms. In the æstivo-autumnal type, the parasites are concentrated in the spleen and bone marrow and it is only during the youngest stages of the parasite that the infected cells circulate freely in the peripheral blood. Perhaps one of the most striking and most perplexing examples of all is the profound variation in the case of infection with *Filaria nocturna*. This distribution of pathogenic organisms should be borne in mind in attempting the transmission of infectious diseases to lower animals.

Interpretation of Leucocyte Counts.—The consideration of the distribution of cells in the circulating blood is of significance in the interpretation of leucocyte counts. As early as 1892 it was suggested by Rieder,[8] and a little later by Schulz,[9] that the ordinary leucocytoses are due, not to an increased production of white cells, but to a redistribution of them, the cells from the blood spaces being called out into the peripheral circulation at the time of an infectious process. Although this view certainly does not apply to all cases, there are many instances in which it is seen that sudden changes occur in the leucocyte count which are due, not to the formation or destruction of cells, but to a redistribution of the cells in the body. Löwit,[10] in 1892, expressed the prediction that a leucopœnia probably preceded the leucocytosis in many infections, in a manner somewhat analogous to these experimental leucopœnias and leucocytoses. This view received prompt confirmation by Sherrington,[11] and others. There are numerous examples of the development of a leucocytosis, under clinical conditions, in a space of time much too short for the production of new cells. In intestinal obstruction there is often a sudden outpouring of adult polymorphonuclear cells, producing a rise in the white count to 30,000 cells, or more, within five or six hours. Furthermore, there is the example, previously mentioned, of the doubling of the leucocyte count in a few hours after a cold bath. Although the exact time required for the multiplication of some of the lowest types of bacterial cells is extremely short, yet it is obvious that the sudden changes in

the number of blood cells are not due to a destruction and formation of corpuscles, but to a redistribution of cells already existing in the body. At the beginning of an acute leucocytosis the polymorphonuclear cells which appear are mature in their morphology and do not have the appearance of being young and freshly formed. Similarly, in the experimental leucopœnias there is no reason to assume a sudden destruction of leucocytes; the injected material in most instances is not toxic *in vitro* for leucocytes and there is no evidence in the morphology of the leucocytes of any toxic action *in vivo*.

The preceding data afford ample ground for the conclusion that the leucocyte counts must be considered as indicating only the number of cells at a given time in the peripheral circulation and not as an index of the absolute number in the entire body. Thus, it is not justifiable to conclude, *a priori*, that there is a destruction of leucocytes in typhoid fever. The leucopœnia which develops might readily lead to the assumption that there is an extensive destruction of white cells. The observations of Thayer,[12] however, show that a mild physiological stimulus will promptly raise the number of leucocytes at least to the upper limits of normal. As far as the leucocyte count of the peripheral blood in typhoid fever is concerned, it is obvious, on theoretical grounds, that the absolute number of leucocytes in the body may be either diminished, normal, or increased. The determination of the exact condition must be made by means other than the examination of the circulating blood. The evidence bearing on the question is very meager, but, as far as it goes, it would seem at least possible that the absolute diminution of leucocytes in typhoid may be much less than one has ordinarily supposed.

Moreover, the infecting organism is not the sole factor which influences the white cell count. It is well known that the severity of the infection is important. Thus, pyogenic organisms, which ordinarily produce a leucocytosis, may, in hyperacute infections, produce a leucopœnia; if one accepts the work of Sherrington this would mean that the initial leucopœnia which often occurs very early in the course of a pyogenic infection may persist in the severe cases instead of giving place to a leucocytosis. There is also another factor which requires consideration; Emerson [13] has noted that the same organism may produce different effects, according to the location of the lesion in the body. Thus, in the after effects of typhoid fever, a peripheral lesion such as may occur in the bones is accompanied by a leucocytosis. This also affords an instance in which typhoid infection is not accompanied by any manifest destruction of leucocytes. Tuberculous infections also indicate that the location of the lesion in the body rather than the infecting micro-organism may sometimes be a determining factor in the effect on the leucocyte count. Thus milary tuberculosis may be accompanied by a leucopœnia, whereas tuberculosis of the meninges usually produces a leucocytosis. The examples afforded by tuberculosis, however, are often complicated by the possibility of secondary infection. Apparently there is no crucial experimental demonstration of these clinical observations that the location of the lesion may occasionally be the determining factor in the leucocyte count.

PART II. SPECIAL CONSIDERATIONS REGARDING THE TRANSMISSION OF INFECTIOUS DISEASES

It would seem that the diseases to which lower animals are naturally susceptible by intravenous, subcutaneous, or intraperitoneal inoculation have already been determined, at least for the more important infections. A further extension of the ability to transmit diseases to relatively insusceptible species would, in most cases, involve either a modification of these simpler methods of inoculation, or special preparation of the new host. There are many arguments which may be advanced against intravenous injection. In the first place, there is necessarily considerable dilution of the infective material with an extremely good opportunity for the operation of any deleterious action which the plasma and cells of the blood may possess. *A priori*, intravenous injection would seem to be ideal in its possibility of reaching all the organs of the body. However, the foreign material is not only collected primarily in the lungs, liver, and spleen, but the phagocytic cells of the blood also collect in these areas. Moreover, the mechanical disadvantages are not inconsiderable, since the material introduced must be reduced to a fine suspension on account of the danger of embolism; even with a fine emulsion, massive injections for the purpose of overwhelming an animal are often inadvisable on account of the danger of immediate death.

In recent years, not a little attention has been given to the concentration of infective agents in locations of special susceptibility just as therapeutic agents are introduced at the principal site of local infections, as in the routine intraspinous treatment of cerebrospinal meningitis, and in the treatment of tabes by Swift and Ellis.[14] It seems logical to introduce the infective agent into the locations which are involved in spontaneous infections, as in the case of the experimental production of anterior poliomyelitis by inoculation into the central nervous system, or the reproduction of tuberculosis and syphilis by inoculation into the testes.

CHOICE OF THE SPLEEN FOR INOCULATION EXPERIMENTS

An attempt has been made to take advantage of some of these special methods of inoculation in some experiments on the transmission of leukæmia to lower animals. For the inoculation of lower animals, the spleen was selected as the site of injection, not only because this organ is involved in leukæmia, but because it frequently harbors various parasites. At the same time it cannot be regarded as a site of especially low resistance in view of the opportunity for the action of the fluids and cells of the blood in its sinuses and also on account of the phagocytic cells characteristic of the spleen itself. Nevertheless, it is a convenient location for concentrating a large amount of infective tissue in preference to the injection of a comparatively few isolated cells into the blood stream. The spleen is easily exposed by a laparotomy done, of course, under ether. In some animals, especially in cats, it was found that large blebs of the injected material, measuring 1 or 2 cm. in diameter, can be produced under the capsule of the spleen. Since these blebs are not rapidly absorbed, their contents would naturally be much better protected from the immediate

action of the blood serum and the leucocytes than they would in the case of intravenous injection. There is also considerable mechanical advantage in making injections directly into the spleen; large pieces of tissue, such as would be altogether unsuitable for intravenous work, can be introduced into this organ. The spleen readily filters out the grosser particles; in a large number of instances we have had no evidences of embolism in the injection into the spleen of coarse suspensions of various tissues.

From a clinical standpoint the spleen of some animals, notably the monkey, is an excellent organ for observation, since its size can be easily determined by palpation, thereby enabling one to detect very readily a splenomegaly. The advantage of this is evident, both in those cases in which a change in the blood picture occurs, and also during any intervals in which the blood picture is normal while the spleen is enlarged.

Direct inoculation into the spleen and other organs has been practised in a variety of conditions. Musgrave and Clegg [35] attempted to produce amœbic hepatitis by direct injection into the liver of cultures of the limax group growing with *B. typhosus*. Mackie [36] inoculated *Leishmania tropica* into the liver and spleen and v. Seht [37] reported the inoculation of leukæmic blood into the spleen of monkeys. All of these injections into the viscera resulted negatively. Patton [38] obtained some positive results by the direct inoculation of *Leishmania donovani* into the liver.

INOCULATION EXPERIMENTS IN LEUKÆMIA

Our own work has been confined to the inoculation of material from various types of splenomegalies into several species of animals. For the most part we confined our attention to acute and subacute leukæmias. There is considerable choice in the selection of material for inoculation. In the patients who were studied, we have used blood for inoculation as a routine, and in one instance some enlarged glands. No patients were available in whom the spleen was enlarged in a suitable manner for puncture and aspiration. In one autopsy case, splenic tissue was obtained for injection. In all, five cases of leukæmia were studied; from four of these blood was injected into the spleen of cats, monkeys, and rats. There was frequently considerable disturbance of the blood picture during the first two or three weeks after the injection. The most prominent characteristics were a rise in the leucocyte count, the appearance of unusual cells in the circulation, and frequently an increase in the number of platelets with the appearance of many large forms. Injection of normal blood did not produce such changes. The effect of leukæmic blood was not constant, however, and in no case did it produce a picture of leukæmia. In one instance enlarged glands from a case of acute leukæmia were injected but no definite effect was produced. At most the results were never more than suggestive, and consequently a full report of these cases will not be made at present. One case which came to autopsy, however, deserves special consideration.

ACUTE LEUKÆMIA

This case was seen through the kindness of Doctors Leopold and Sexton at the Hebrew Hospital. The patient was a man in the thirties, of rather robust constitution. The total course of his disease was of only a few weeks' duration and he came to the hospital in the last few days of his illness. On admission he was semicomatose and presented at this time the typical clinical features of an advanced pernicious anæmia. There was a moderate degree of jaundice. The spleen and liver were not palpable. The blood picture, however, was by no means a simple one.

The red cells were diminished to 1,500,000 per c. mm. and there was a proportional reduction of hæmoglobin. Only a moderate grade of anisocytosis and poikilocytosis was present. Normoblasts and megaloblasts were abundant. The white count was high, varying from 22,000 to 24,000. Of these cells about 2000 were nucleated reds and of the remainder, 60 per cent were polymorphonuclear in type. There were many rather unusual mononuclear cells but only an occasional myelocyte was seen.

There was nothing remarkable about the platelets either in their morphology or numbers.

The case was clearly an unusual one but seemed to conform most nearly to that group of acute leukæmias which tend to go over into a fairly typical pernicious anæmia.

Direct transfusion of blood produced only a very transient benefit, and exitus occurred a few days after admission to the hospital. Five hours after death the spleen was removed; it was only slightly enlarged. Aërobic and anaërobic cultures of small pieces of splenic tissue on ascitic fluid, blood serum, Dorsett's egg medium, blood agar (NNN medium), and milk, remained sterile for a period of three weeks. A coarse emulsion of the spleen in salt solution was injected into some animals. The following is a general summary of the results which were obtained.

A cat inoculated into the spleen died on the sixth day after injection. The spleen of this animal was inoculated intrasplenically into a young adult cat which died on the sixth day after injection. Subinoculations were made intrasplenically into a monkey from the spleen of this cat. Three weeks later the spleen of the monkey had increased to several times its normal size and the blood picture was characteristic of lymphatic leukæmia. The temperature of the animal was high being 104° and 105°F., but this is not very unusual in normal monkeys. Splenic tissue removed at this time failed to produce any change in a second monkey. The blood picture returned rather rapidly to normal, but the spleen remained large for many weeks. This animal died 15 months later. The autopsy revealed no apparent cause of death. The protocols of these experiments are as follows.

A monkey and a cat were injected intrasplenically with the patient's spleen. This material was highly toxic for the monkey, death taking place within two or three minutes after the injection from cardiac failure. The cat recovered from the operation but became somewhat ill in a few days, coma develop-

ing on the sixth day after injection. Blood smears taken when the animal was in complete coma showed a remarkable picture in that the leucocytes were practically absent. The ordinary preparation for leucocyte counting showed no cells in a 0.1 sq. mm. unit. Blood cultures on milk showed a growth of a micrococcus in one of three tubes, indicating a secondary bacterial invasion. This animal was sacrificed just before death and subinoculations were made, spleen, blood, and bone-marrow being used, one cat being employed for each substance. All of the animals remained perfectly well except the one receiving an injection of spleen. This animal died on the sixth day and blood smears made a few hours before death also showed a complete absence of leucocytes. This is open to the interpretation that in the acutely fatal cases some leucotoxin produced extensive destruction of the white cells. A simpler explanation, however, suggests itself, since in some instances control animals injected with large doses of bacteria also showed when in the stage of coma a similar absence of leucocytes. Cultures from the heart blood of this second cat showed prompt growth on milk. The spleen itself showed no gross changes; small portions were emulsified and injected into the spleen of a monkey (*Macacus rhesus*). This cat died after three days from a complicating peritonitis whereas the monkey remained apparently well. The operative incision healed promptly with no evidence of any secondary infection. The white blood counts showed some fluctuation, but no significance could be attached to them. The count fell at first from a normal of 27,000 to 13,000. During the next three weeks it rose gradually to 56,000, a significant change occurring in the differential. In this species of monkey, the mononuclear elements are normally very high as compared with man; a typical count of this individual before injection showed 35 per cent polymorphonuclear cells, and a total of 57 per cent mononuclears with 8 per cent of cells unclassified. During the rise in the white count, however, the polymorphonuclears fell to 19 per cent, and the mononuclears rose to 81 per cent. Taking fully into consideration the normal blood picture of the *Macacus rhesus*, the smear was distinctly characteristic of a leukæmia of the lymphatic type. The evidence of a leukæmic change as contrasted with a leucocytosis was seen, both in the low percentage of polymorphonuclear cells in the blood and in the appearance of some immature cells, such as a few myeloblasts. These cells were not found in the normal blood of this individual before injection and in the examination of 10 other macacus monkeys they occurred only in a few individuals and in very small numbers. This change in the blood picture lasted for several days and then returned to normal. In addition to the change in the blood picture a well marked splenomegaly developed. Three weeks after the injection, the spleen was found to be several times larger than its normal size. On exploration, this increase in size was found to be due, not to swelling and congestion, for the spleen was hard and firm, measuring four times its size before injection. On surgical extirpation of about one-fourth of the organ, it was so firm that relatively little hæmorrhage took place. Histologically there was nothing remarkable.

This splenic tissue obtained by operation was injected into the spleen of a monkey and into a kitten. Cultures were also made on blood agar, on ascitic fluid containing fresh tissue and on Dorsett's egg medium. The animals remained well. During the next three months no significant change occurred either in the blood count or in the size of the spleen. The cultures were observed for three weeks but no growth developed.

Some control observations were made in order to determine as accurately as possible the cause for the enlargement of the spleen and the change in the blood occurring in the monkey. It is important to eliminate the ordinary bacterial causes especially secondary pyogenic infection and tuberculosis.

Apparently a few bacteria were present in the cat's spleen which was injected into the monkey, since the blood of this cat showed growth in milk of a coccus. This is an unfortunate circumstance but secondary infection in a moribund animal readily develops. These organisms apparently were not present in the patient's spleen since the cultures on various media showed no growth. There is considerable evidence that this organism could not have been responsible for the change observed in the monkey. An absolute increase in mononuclear cells is not a characteristic of pyogenic infection; and moreover there was no evidence of any local or general sepsis. Finally a control experiment was done injecting 2 c. c. of a milk culture of this micrococcus into the spleen of a normal monkey. A typical pyogenic leucocytosis resulted. The leucocytes rose in 24 hours from 8000 to 10,000 and the proportion of polymorphonuclear cells rose from 36 to 95 per cent. The blood picture gradually returned to normal and the spleen did not enlarge. Ten months later this animal developed several metastatic abscesses. The spleen did not enlarge and the white count rose to 59,000 with 90 per cent polymorphonuclear cells. He soon recovered from these infections.

If there were any evidence by which the production of the leukæmia picture could be ascribed to the bacteria present, it would be an extremely interesting factor in bringing about the correlation of the leucocytoses with the leukæmias, since the hypothesis has been advanced that the two conditions are part of the same process, and that the same agent, if allowed to act for a long period, may produce first a leucocytosis, and subsequently, with the exhaustion of the bone marrow, a leukæmic picture may develop.

The consideration of tuberculosis is important and fortunately it can be excluded rather readily. In the first place this monkey developing a splenomegaly, lived for many months after this experiment and when death eventually occurred, the autopsy showed no evidence of either active or healed lesions of tuberculosis. Moreover, when the spleen had reached its maximum size, a portion that was excised showed no histological evidence of tuberculosis and no growth developed on appropriate media. A second monkey inoculated with the tissue did not develop tuberculosis.

From the data which have been presented the conclusion naturally follows that the enlargement of the spleen accom-

FIG. 1.

FIG. 3.

FIG. 2.

panied by the leukæmic blood picture could not be attributed to pyogenic infection or to tuberculosis.

This leukæmic change was of short duration and could not be transmitted by subinoculation. Nevertheless it is of interest in view of the many entirely futile attempts to produce either leukæmia or splenomegaly experimentally.

It is perhaps a little difficult to form a distinct impression of the difference in these blood pictures simply from an analysis of the total and the differential counts. Accordingly we have reproduced typical fields from three of the more important preparations: namely, of (1) a normal monkey; (2) the same monkey after injection with material coming originally from a case of leukæmia in man; and (3) the reaction of a monkey to pyogenic bacteria.

SUMMARY

I. The circulation of normal and foreign substances in the blood often fails to follow mechanical laws, either under normal or pathologic conditions. An unequal distribution occurs which is governed by biological conditions. The corpuscles of the blood are not distributed with mechanical uniformity throughout the blood channels; parasites invading the blood stream are often concentrated in the blood spaces of the viscera.

II. Upon injection of a variety of substances into the circulation, the injected substance and the leucocytes, especially the polymorphonuclears, disappear from the peripheral circulation within a few minutes and collect in the blood vessels of the viscera principally in the lungs and liver. Within a short time the leucocytes return to the peripheral circulation, often in increased numbers and sometimes after having phagocyted the injected material.

III. The leucocyte count cannot be interpreted as an index of absolute change in number of leucocytes in the entire body, for it often indicates only changes in distribution rather than a formation or destruction of white cells. Thus, the total white count does not constitute crucial evidence that there is an absolute leucopœnia in typhoid fever. There are at least three factors governing the leucocyte count; namely, (1) the infecting organism; (2) the severity of the infection; and (3) the location of the infection in the host.

IV. The failure of foreign substances to be distributed in the blood stream according to mechanical laws has an important bearing on the transmission of infectious diseases. It offers many arguments against intravenous injections of infective material for the transmission of a disease to resistant animals for the reason that,

1. Considerable dilution of the material necessarily occurs.

2. Extensive opportunity is offered for the action of any deleterious effects which the fluids and cells of the blood may exert.

3. Fine suspensions and limited amounts of material are necessary in order to avoid embolism and sudden death.

4. Finely suspended matter is not distributed equally throughout the blood stream, but a large proportion is removed by the lungs.

Many of these objections could, of course, be overcome by an intra-arterial injection if it were made into the proper side of the circulation.

V. Inoculation into the spleen for the transmission of splenomegalies to lower animals possesses certain advantages:

1. It avoids many of the disadvantages of intravenous injection.

2. The injected material can be temporarily protected from the immediate action of the fluids and cells of the body.

3. The mechanical advantage is considerable, since large pieces of material can be used.

4. The spleen is well adapted for study, since changes in its size in certain animals can be readily determined by palpation.

VI. Inoculation of the spleen of a case of acute leukæmia into the spleens of cats produced death acutely. Inoculation from these cats into a spleen of a monkey produced a chronic splenomegaly with an acute temporary leukæmic change in the blood picture. The production of even abortive leukæmic changes and of splenomegaly in a normal animal by inoculation of human material is of interest.

This work was conducted during 1914 in the clinic of Prof. Lewellys F. Barker at the Johns Hopkins Hospital. A report was made at that time before the Johns Hopkins Medical Society. In the meantime the continuance of these studies has been seriously interrupted and has finally been suspended for the time being. Consequently, it has seemed advisable to make this incomplete report without waiting for confirmation and extension of these results. It is a pleasure to thank Dr. Barker for a helpful and stimulating interest.

DESCRIPTION OF ILLUSTRATIONS

ROMANOWSKY STAIN (WILSON'S)

FIG. 1. Typical field from blood smear of normal monkey.

FIG. 2. The same monkey three weeks after inoculation with splenic tissue from an animal injected with the spleen from a case of leukæmia in man.

FIG. 3. Control monkey inoculated with pyogenic organisms to show the effect on the blood picture.

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MEMORIAL MEETING TO DR. THEODORE CALDWELL JANEWAY

A memorial meeting for Dr. Theodore C. Janeway, late Professor of Medicine to The Johns Hopkins University and Physician-in-Chief to the Hospital, was held in the hall of the Engineering Building of the university at Homewood, on Sunday afternoon, March 10. The meeting was opened with prayer by Rev. Dr. Arthur B. Kinsolving, and addresses were made by President Frank J. Goodnow, Johns Hopkins University; Mr. B. Preston Clark, Boston, Mass.; Dr. John Howland, Johns Hopkins University; Dr. Alexander Lambert, Dean of the Medical School of Columbia University; Dr. David Edsall, Harvard University; Major General William C. Gorgas, Surgeon General, U. S. Army, and Dr. William H. Welch, Johns Hopkins University.

Rev. Dr. Arthur B. Kinsolving.—O God our Father, from whom we come, to whom we go, in whose gracious protection Thy children abide in whatsoever place and condition they may be; we thank Thee for all the goodly company of those who have helped us by their eminent labors and noble examples.

We yield unto Thee high praise and hearty thanks for the graces and virtues of him we are met to memorialize, for the beneficent skill of the good physician, for the diligent man of science and research, for the fearless follower of truth, for the strong and inspiring friend, for the devout Christian who amid his thronging duties made room in his life for God, for the citizen who withheld not his life at his country's call.

Help us each to grow stronger, more gentle, brave and true by calling to remembrance his gifts of thought and speech, his quick and understanding sympathy, his vision of service, and duty. Grant that all that he was here may be ripened and expanded there, and that he may find employment in the spacious fields of eternity.

Help us all, O God, to rejoice more and more in other men's strength and brightness and success, and set our hearts free to serve Thee better, and more perfectly to love Thee,

Through Jesus Christ our Saviour.

President Frank J. Goodnow.—We have come together this afternoon to honor the memory of Theodore Caldwell Janeway whose death in the service of his country has caused such a vacancy in our ranks.

Prior to the breaking out of the war, to the prosecution of which Dr. Janeway gave so much of his time and strength, he had won an enviable reputation as practitioner, teacher, organizer and student. His love for the scientific side of his profession was so great that when the opportunity presented itself he gave up active practice to devote his entire time to teaching and investigation. At the time this country entered as a participant in the great conflict now raging, he had succeeded in putting his department in the Hospital and Medical School in a state of rare efficiency.

The call of his country could not, however, be denied. The extra duties which he then assumed were a great addition to already burdensome responsibilities. His regretted death cut him off at the height of his usefulness. It leaves us, his friends, however, with the consolation that the standards he set will live long after he has gone out of our lives. We mourn the loss of a kindly presence. We cherish the memory of a sincere personality, a strong character, an able man.

Mr. B. Preston Clark.—It is entirely natural that we who know and love Theodore Janeway should each know best some special side of that nature, which touched life so profoundly, and from so many angles.

Though he and I have known each other for less than ten years, it seems as though we had always known each other.

My first meeting with him was after a remarkable diagnosis. The patient, one of my own boys, was recovering from a serious illness. I tried to express my gratitude as best I could, and in that quick way of his he said "Most of the agencies that make for human health and disease are microscopic in their character, and we really know very little about any of them." That attitude of simple humility toward the profession of which he was a master I can never forget.

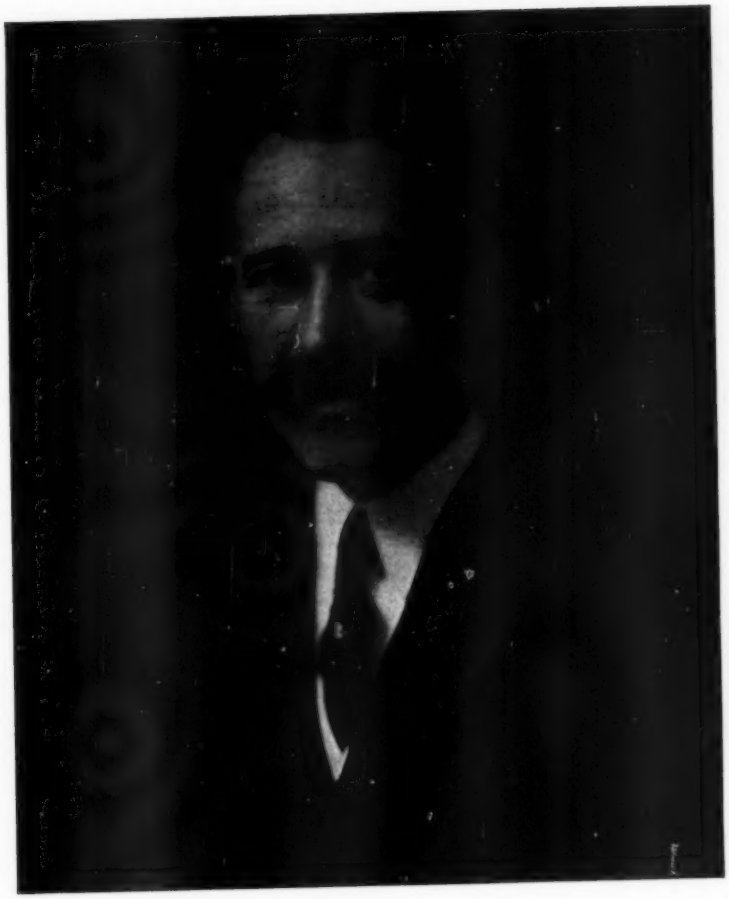
I have not the knowledge, as so many here to day have, to gauge in any broad way his professional skill, I being only a layman, a business man. I only know that it must have been wonderful. It has been on other sides that I have known him.

When some difficult and intricate industrial problem has been under consideration, I have taken the opportunity when it was possible to discuss it with him. And we never had such a discussion without my learning much from his method of approach which helped to clarify the issue and to assist in finding a solution. For his mind had a universal quality.

Of just one other quality of his vivid personality I shall speak and only one. And that is his apprehension of the invisible and the spiritual as being more truly real than aught which we can touch or handle. That is to me the crown of his personality and its very essence.

During this last summer on his short vacation we lost no moment when we could be together, and the same was true on my own hurried trips to Washington during the early winter. And always I was conscious in him of a great and increasing power of leadership.

Leadership is a subtle and elusive thing, not to be limited or exactly defined. But of one thing we can be sure. The



Reed Hemenway.

great leader cares so deeply for his cause; he sees his vision so clearly, that he forgets himself. He sacrifices himself without knowing that he is doing so; he sees in sacrifice simply boundless opportunity. He draws men after him; because they follow, not him alone. They follow that which he follows. As in the battles of old the fighters followed the gigantic shadowy warrior who led them to victory.

And when in battle a leader, a true leader, falls, the charge checks for perhaps a brief moment, but it goes forward with undiminished power, and the charge is driven home.

Such a vision of the invisible and the eternal was given to Theodore Janeway; such a leader he was and is; and may it be given to us in the light of that vision to follow that which he followed; to raise aloft the standard which has fallen from his hand; to see in sacrifice simply opportunity; to live worthily of the vision, to close up the ranks, and to carry the charge home. Thus shall we pay a living tribute to a great leader, and a yet greater man.

Dr. John Howland.—For many years I have known and admired Theodore Janeway. We were boys together at school, we were at college and in the medical school at the same time, we were contemporaries in New York and, finally, were colleagues in Baltimore together. I may speak of him, then, in many stages of his career, for I saw him grow from a schoolboy into a man and finally become a leader of medicine.

On looking back, it is easy to see that he exhibited strikingly as a boy the qualities that made him distinguished as a man. There was nothing that he had to put behind him or forget or outgrow, nor was there an abrupt change from the irresponsibilities of youth to the duties of later life. It was just a gradual, even growth and development in a life of singular rectitude.

He was, in school and college, conscientious, persevering and serious. He matured early. He was studious and always a hard worker but there was nothing of the book-worm about him. He was merry and keen in regard to all the activities of school and college life. Cheerful and well liked by all, he gave the gift of his intimacy to but few.

Thus, Janeway went through college, leaving behind an enviable reputation in those courses that prepare for a medical career, for he early knew what his profession was to be, and, alive to the responsibility of one who bears a distinguished name and also because he believed in doing all important things well, he worked with characteristic diligence and enthusiasm. Those who taught him could outline his future.

It was, however, in his medical school course that he really shone. He was the first or second man in a singularly good class and, by virtue of this fact, became eligible to compete for a number of prizes of very considerable money value. Then he did a characteristic thing, the reason for which was only surmised and of which he never spoke to any one. He did not compete for the prizes. It was quite plain that he would have been successful and he must have known it for he judged fairly his own abilities though he never overestimated them. But he knew there were others who needed the reward more than he. Such consideration for others was not an isolated example. It was a constant and conspicuous trait of a generous spirit, exhibited throughout his whole life.

He served through his hospital years with great credit and then began the practice of medicine with his father. It is seldom that any one is fortunate enough to work under such inspiration and guidance. Dr. Janeway, the elder, was a medical man in a generation. He had intuition, great knowledge, his experience was enormous and his judgment unerring. Between him and his son there was complete community of spirit and entire intellectual sympathy.

It is one of the regrettable things in medicine that a master of diagnosis cannot transmit his experience to succeeding generations. His knowledge he may, in books and pamphlets; his experience usually dies with him unless the opportunity is given to the pupil, by close and constant association, to see repeatedly the attitude of mind toward medical problems and thus to absorb some of the mental processes of the master. This opportunity was given to Theodore Janeway and was eagerly utilized. The years that they were together must have been a period of intense enjoyment and a wonderful experience for both father and son. They were absorbed day after day in entire accord upon the work that interested them most.

It was a period of rapid growth for Theodore Janeway, so rapid that it became in a short time evident to all his contemporaries that he was to be a man of prominence and this conviction steadily grew; for it was readily recognized that he was not only a diagnostician of great skill, always sound and often brilliant, but that he was a capable experimenter and an especially gifted teacher.

He began to teach first in a minor capacity at The University and Bellevue Medical College and later he advanced to more important positions until he finally was called to the Bard Professorship of Medicine at the College of Physicians and Surgeons.

To all forms of teaching he added something new, something that made the subject more interesting, more stimulating. In the teaching of physical diagnosis, he introduced simple mechanical experiments to demonstrate the principles of physics underlying the signs. He was the first in New York City to teach medicine from the standpoint that disease is a deviation from the normal physiological basis and he, together with Oertel, introduced, at the City Hospital, the clinical-pathological conference, a form of exercise that has been widely adopted. And it should not be forgotten that in this country the clinical study of the blood pressure began with him and that he devised the first instrument that made the study of this possible for us at the bedside.

Janeway, at one time or another, was connected with a number of different dispensaries and hospitals. Many of the services he reorganized and all were improved by better methods, greater service and more complete cooperation. When he went to the City Hospital on Blackwell's Island, the service was neglected, the internes were poor in ability and hard to obtain. In a short time, everything was changed so that it

was an active, most effective organization with men eagerly striving for positions upon his staff.

Occupied as he was with teaching, research, hospital work and practice, he, nevertheless, found time to give advice and assistance to the charitable organizations that try to improve the conditions of those incapacitated for work by accident and disease. He appreciated the distress that frequently accompanies disease and he felt that he could and would contribute to an intelligent amelioration of this. For many years he was closely identified with the Association for Improving the Condition of the Poor.

In all his work, indeed in all his life, he was as conscientious as a man could be. He was thoughtful of others, he made the way easier for many but he would not spare himself. He worked incessantly and constantly beyond his physical capacity. He could not be persuaded to do less. It was part of his creed that if things were to be done, they were to be done well no matter at what cost to himself. He was mentally sound and he was ruggedly honest with all and especially with himself. He practiced medicine and he taught medicine honestly. If there were an error in diagnosis, he was always the first to acknowledge it; he would claim no part in any work that was not his own, and he could teach medicine only upon the basis of established fact. To those who knew him, he was a loyal and devoted friend, a companion full of humor but also of inspiration. And so I felt and shall always feel that when Theodore Janeway died, at the height of his ability and usefulness, medicine suffered a grievous loss and a splendid man was gathered to his fathers.

Dr. Alexander Lambert.—In New York we of the medical profession have never ceased to look upon Theodore C. Janeway as one of us and to regard him as a New Yorker. Outside of the profession the city still asks for him for advice although he has been away from his inherited professional haunts for nearly four years. New York has never been without a Doctor Janeway for more than fifty years and that city, in spite of its two hundred new citizens each day, is a city of habit and tradition especially in medical affairs. A consultation with Doctor Janeway was a habit so ingrained that it is not yet quite broken, at least in the thought and subconscious longing of the population. This habit was founded by Theodore Janeway's father who won the position of first consultant in New York by giving a careful study to each problem presented to him before drawing upon his remarkable experience in the pathological amphitheater and the clinical wards of the three great hospitals which he had served.

New York medicine, to a superficial view, often seems tainted with commercial methods, harassed by professional competition and hampered in development because its successful practitioners of the medical art are broad catholic citizens of the world and not intensive scientific investigators. Such a judgment is truly superficial for the influence of New York has been widely spread through the United States by the activity in the teaching hospitals of the city of certain great personalities who stood for an ideal to make the practice of medicine a humane art applied to human beings by human beings.

Both Janeways, father and son, represented this class in the metropolitan community—Edward G. Janeway exerted his greatest influence in this broad New York way upon many generations of students from all the colleges of the city and from many outside of it as a physician of Bellevue Hospital and not in any narrow field limited by academic walls.

Theodore C. Janeway inherited a remarkable memory which he trained to store up both the facts to be found in medical literature and also the varied clinical pictures that were constantly being brought to his father's office for interpretation. In that office under that chief he developed a great diagnostic insight which however he never allowed to lead him across lots to his goal without first exhausting every known method of physical and laboratory study. He was a hard taskmaster to himself both as a practitioner and as a consultant and left no step unconsidered which would assist his fellow worker and colleague or be of assistance to the sick and ailing patient. Theodore Janeway was trained under the exacting conditions of a large consulting practice in a large city. He nevertheless never became commercial and showed a remarkable aptitude for applying scientific methods to the study of clinical medicine and for stimulating others to pursue a career in the research laboratories connected with his hospital wards. His ability in this field has meant much to New York in general and to the College of Physicians and Surgeons in particular.

It was the special opportunity of the college to call Theodore Janeway to the career of a teacher in a broad field and to raise him at one step from an instructorship of associate grade to the highest position in clinical medicine within the gift of Columbia University, the Bard Professorship of the Practice of Medicine. He succeeded in his task from the outset and became widely known in New York and the whole country as a teacher who could analyze the process of reasoning which led to his diagnosis, who possessed the art of graphic description to an unusual degree and who instilled in his students and in the instructors of his department a rigid thoroughness in routine and an exact precision in thought and expression.

As an executive Theodore Janeway was familiar with every detail of his department. He was always accessible to his colleagues for counsel and eager to consider advice from an assistant as from an equal. He was earnestly devoted to his conception of the right and ready to fight or to make any personal sacrifices for his ideals. He left his mark on New York medicine by taking charge of a department bare of every facility for modern teaching and research and after a short four years he left it equipped with a library, which had been his own, with a hospital service, with research laboratories and with the nucleus of a staff devoted to teaching and to research. Columbia University and New York were that much poorer when he left to assume the work in Baltimore at Johns Hopkins.

There are in New York many younger men in the profession who have impressed on me, since the untimely death of Theodore Janeway, their sense of personal loss and their gratitude to him for an early insight into the high ideals of medicine,

for an appreciation of the necessity for absolute medical honesty and the need for a constant revision of opinion as new facts are discovered and for having labored with a man devoted to a thorough and systematic habit of work.

It was my personal privilege to start Theodore Janeway as a student on his medical career and to be among the first to teach him, to whom I later went to learn. It is my present privilege to add my testimony to his worth as a clinician, to his ability as a teacher, to his loyalty to his friends and to the permanent impress for good which he made on medical education in New York City. His work and character are remembered there as an exponent of all that is good and all that is best in a profession which is still controlled by ideals; a profession which is still advanced by the power of the human brain and hand to do the most perfect work in a world so largely controlled and ruled by the machinery of construction and of destruction.

Dr. David Edsall.—In periods of great change in thought and policy and in the nature of individual responsibilities clear vision, high purpose, and a determined idealism tempered by wide judgment, are qualities of such importance as to overbalance others. Doubtless in all times of great activity and change in work of whatever sort these qualities have seemed to be needed as never before. We should not do justice to our forbears in medicine if we exalted too far above theirs the tasks that have fallen upon those to whom we have looked for leadership, but we nevertheless can but believe that in the past two or three decades, the complexities and responsibilities of medicine have been largely added to and there have been in progress and in prospect such fundamental changes, not only in knowledge but in policy, that qualities and training fitting for wise guidance have been especially demanded and more desirable than any others. And in recent times the greater weight of these new responsibilities has fallen upon clinicians, for the non-clinical branches had passed through their most acute travail earlier and had become somewhat adjusted to the changes when the clinician met the need of a new alignment in viewpoint and in manner of life and thought. To the clinician the complexity has been increased by the need of retaining much that his colleagues could cast off and nevertheless of readjusting his methods in much the same manner as they. He has had to add a multiplicity of precise methods to the earlier less exact ones that demanded chiefly training in observation and interpretation, but he has been obliged to retain undiminished his regard for the latter. He has had need to undergo the still more difficult mental adjustment to experimental instead of observational methods of thought and especially of research, as the yield from the older methods became less fruitful; and yet he has had to retain a cautious respect for even purely empirical observations. In academic medicine he has had to make decisions and adjustments similar to those of his colleagues in the distribution of his energies and in manner of life, but he has had to cherish and to train equally the power of human understanding and the patient study of character and the attention to petty affairs that are so spendthrift of time and energy, but without which he would overlook his main duty, the safeguarding of individual human life and health.

These changes have been of gradual growth but Theodore Janeway passed through the period of most rapid transformation, the period in which alterations have been at times so sudden and radical as to arouse wide differences of opinion, and in which clear judgment and determination have been needed to avoid undue haste and enthusiasm as against complacent inertia.

Long training with his distinguished father and a very lovely veneration of him would of themselves have sufficed to prevent him from being led by enthusiasm for the newer types of study to belittle the value of those methods that made Edward Janeway so eminent. But by temperament as well, Theodore Janeway was conspicuously attached to and he was rarely gifted in the painstaking clinical and pathological observation of disease, and through years of accumulated study of literature of disease in its progress and of its pathological results, he acquired that skill and clarity in the observation and discussion of matters of diagnosis and treatment that left no one his superior as a clinician or as a contributor to directly practical clinical medicine and gave him his exceptional strength as a teacher of practice.

Clinical medicine, especially in its research activities, was coming constantly closer to the laboratory and it was inevitable that this rapprochement should become increasingly intimate. But general sympathy with this essential movement could be secured early and its progress hastened far more through keen appreciation of what was good in the older methods as well as the new than through a partisan championship of the new alone. It was a great and permanent service that Theodore Janeway rendered to medicine in furnishing so fine and timely and so outstanding a demonstration that a man may be a devoted master in the older methods and at the same time an eager student and contributor in the new, and likewise a stimulus and guide equally to those whose pathway leads them chiefly into the one or the other and especially to those who would co-ordinate the two. Nothing has been more needed. No one has done it so well. To have had great opportunity and power to exert influence upon the things that mould the character of one's profession and to have used them so as to have left debtor both radical and conservative is a singularly rare and valuable service. His success in this was in part due to the training and judgment that I have indicated, in part to a very broad fund of knowledge ever at the service of others, but no less than to these it was due to that type of ardent sympathy and idealism that leaves a bit of fire in those it touches. To many who came close to him even occasionally there must stand out as more helpful even than his contributions to knowledge the picture of a nobility of purpose, an abundant sympathy and comprehension, fired by that trace of desire for the unattainable which, when restrained by sanity of judgment, lifts up a leader to reach the attainable and without which even genius secures few disciples; and to those engaged in the study of problems in any branch of medicine there will always remain a keen and grateful memory of the inspiring thought-

fulness with which he constantly kept their work in mind and put at their service as few remember to do anything helpful that came up in his own busy work.

And this catholic sympathy and interest extended beyond his labors for the individual sick and for those who deal with them alone. He comprehended clearly the interdependence of health and of many community problems and of the ways in which the physician may attach himself to social movements and still remain within the fields for which his training fits him. He was one of a very few in medicine to whom those who struggle with these problems turned confidently for wise advice and generous aid and yet he saw clearly the limits as well as the extent of the physician's province in these matters. Peculiarly devoted as he was to the human relations of the practice of medicine, whatever the recompense, it was in very considerable part a great sacrifice to relinquish for purely academic work and increased burdens of administration the grateful intimate personal side of the life of the physician who is chosen by the patient, a loss that he did not cease to feel. But when the choice had to be made it was at once made with sole thought of the way in which he could best meet the needs of medicine. This decision was typical of an attitude of mind that was and will remain a powerful part of his influence upon medicine.

There is a comforting sweetness to those who held him personally very dear in the generous evidence of the breadth and variety of his influence that comes from those in all these varied forms of work that the clinician meets in normal times. Never greatly endowed with vigor he had constantly in civil conditions "ventured life and love and health" ever with the unselfish thought of service. It is but natural that all these should have been ventured again, ventured then, alas, finally, in single-hearted loyalty to his country after having given in this work further distinguished exhibition of skill and judgment in organizing and placing men and in the determination of methods and policies.

To have been a wise and trusted pilot in his high calling, to have helped signally to weld together opposing and disorganizing forces, to have guided clearly juniors and contemporaries not only in deeds but in motives, and to have left a light burning in all the forms of his high endeavor, to have done all these is to have done more potent things than are often done.

A thought that has become commonplace through repetition may still seem new and moving when we recall it as we first met it. When I think of the problem of immortality, I always go back to my boyhood to the time when I heard a cold, repressed, unreligious man, after listening apparently uninterested to a discussion of such matters, say suddenly and with a sternness that still arrests my attention that whatever one feels about a future life, immortality of some degree and kind is inevitable for all of us, that we can not prevent the indefinite perpetuation of our influence for good or evil even though the source of the influence may soon become untraceable and unnamable.

"Not till the hours of light return,
All we have built do we discern."

If we can visualize the increasing growth of the wave from an impulse as it passes on from group to group we may find recompense for the unaccountable brevity of a high career in the enduring influence of a true and strong force that will still act when other more prolonged energies have become relatively spent and inert.

Major General William C. Gorgas, Surgeon General, U. S. Army.—My acquaintance with Dr. Janeway began originally when he was a little child. In the early days of my medical career I was house physician in Bellevue Hospital and in the division over which Dr. Janeway, Sr., Dr. Flint and Dr. Lusk presided, three names to conjure with in the province of medicine.

The elder Dr. Janeway at that time was much interested in the pathological work of his division, and it was my duty there to be associated with him and to assist in his researches. Through my visits to Dr. Janeway's house, I first met the younger Dr. Janeway, as I have said, as a little child. In after life I met him occasionally at the meetings of medical societies and other gatherings of our profession. At that time I knew him only as an eminent professional man.

On the entry of our nation into the present war, it became necessary for my office to find men prominent in civil life, above the average mark in their profession, to assist in the selection of those who were to serve as my staff in building up the large machinery which is necessary in the conservation of the health of the armed forces.

I appealed to Dr. Janeway to take over the direction of an important division in the office, and he, as was so characteristic of him, promptly gave up his work in Baltimore almost entirely and devoted himself heart and soul to the furtherance of the interests of his country here in Washington. He was with me up to the time of his death and organized in a most efficient manner the division of which he was the head.

As the head of the Medical Corps, his death was a keen loss to me, aside from the regret which I feel at the death of a friend whom I trusted and admired.

In all the machinery of a busy office, such as ours in Washington, there is not much time for personal intercourse, but I did see Dr. Janeway many times in consultation over matters concerning the routine of his division.

Less than a month before his death, I had occasion to inspect with him some of the southern camps. Our contact at that time was close and intimately personal, for we lived and travelled together for a considerable length of time. Knowing Dr. Janeway in this way personally, for the first time, I was much drawn to him and attracted by the fineness of his character; by his constant cheery manner; his optimistic outlook in the face of any difficulty. The work during this trip was hard and exacting, the days often mounting up to eight and ten hours of constant work; but in the face of it all, he was ever patient, ever alert and always bright and cheerful. I feel that it was a privilege to know in this inti-

mate way the personal side, as well as to realize, as I have for a long time, the fine qualities of his professional mind.

One of the former speakers has made a remark which appealed to me strongly. He has brought up the question as to whether it is altogether regrettable for a man to die in his prime, at the height of his power and vigor and force. In reading military history, I have often thought that no soldier's death was more fortunate than that of Stonewall Jackson, a man who had risen in two years to a position in his profession probably never excelled by any of his predecessors of the English speaking race. His military career had been eminently successful and was markedly so in the battle in which he gave his life for his cause. It had been a day of unexampled success; he had extricated his chief from an apparently impossible position; at the moment when he was stricken down he was following a routed and defeated army; so far as he could see, his course was successful. What greater or more welcome death could a soldier have than to be called at such a time?

Viewed from this aspect, I cannot think that Dr. Janeway's death is altogether regrettable. He was at the prime of life and at the period of exaltation from personal success. He had made his name honored and admired. Of course, we who are left behind see it differently, for apparently Dr. Janeway had within him more years of useful work for his fellow man, and I, as Surgeon General, cannot but feel the loss which his death means in the work to which I am pledged.

But from the standpoint of the individual, if we had to choose our period of death, would most of us take the time when our faculties have begun to deteriorate, when we are old and past the prime, or would we prefer to finish our career when we are strong and sure and in the full vigor of all accomplishment?

And so, today I stand in a double capacity: as the Surgeon General of the Army, I feel keenly the loss of an almost essential part of my organization. As a man and a friend, I feel that sense of personal loss which is inevitable at the departure of those we love.

Dr. William H. Welch.—There is little indeed to add to the tributes which have already been paid to our beloved friend and colleague, Dr. Theodore Janeway. He has been spoken of as the "younger Janeway" and reference has very appropriately been made of his father, who was a great influence in his life. His inheritance, manifested by those remarkable traits of mind and character, was the very best on the paternal and maternal side. His native endowments were high. To those were added an admirable education adapted to his peculiar qualities, and with a view to his profession. He was trained at the Yale Scientific School, and there he followed that course which was in no small part organized and developed by the first president of this university, President Gilman, at the time he was connected with the scientific school at Yale. That was the first course inaugurated which took into consideration the need of specialized training for those who contemplated the study of medicine.

With this inheritance and this training, Dr. Janeway entered upon the study of medicine in New York. He graduated at Columbia University, but his education only then began. It continued through his life.

As I have said the greatest influence was that of his father. Like General Gorgas I also had the privilege of coming under the inspiration of the elder Janeway, who was surely one of the most remarkable men in our profession in our generation, indeed in the medical history of our country. A man whom future generations I think can hardly estimate as we who knew him estimated him, because he was not a prolific writer. His influence was personal and sprang from his knowledge, character and scientific spirit, his absorbing interest and zeal—it was from those qualities he inspired those who came close to him. His services were of the highest character. Every institution with which he was connected received an impression from him.

Dr. Lambert has indicated the great debt which Columbia University and the Presbyterian Hospital owe to Dr. Janeway. While in New York, he also had to do with the working out of the gift of Mrs. Russell Sage, for promoting scientific medicine. While there he was also elected one of the scientific directors of the Rockefeller Institute, to succeed Dr. Christian Herter, and his voice on our board was always most valuable. On behalf of my colleagues on the board of directors of the Rockefeller Institute for Medical Research, I desire to express our sense of personal loss in his death.

He was a good citizen. He was interested in the modern problems of society and although his devotion to his profession was almost single-minded, he did find time to give to some very interesting social questions and there he rendered great service. He was a good doctor and a good citizen.

We were most fortunate in securing Dr. Janeway as the first professor of medicine under the foundation which enabled this university to institute what we believe to be a great reform in clinical teaching. Through the generosity of the Rockefeller Foundation, we were enabled to establish three of our chairs on what we call the "University Basis." The underlying principle is that in the time to come, those who devote themselves to the responsible work of teaching, to the care of patients in the hospital and to research in the laboratory, shall make that their occupation and life work. The principle appealed to Dr. Janeway and although his experience led him to feel there might be some modifications of certain of the requirements, he was himself and always remained heartily in sympathy with the fundamental conception. I think it was always a great satisfaction to him that he was called upon the first to serve in the most important chair in a medical school—that of Medicine—and to develop the clinic along these newer lines. He rendered unforgettable service in this capacity for which the university must always retain a feeling of gratitude.

If I may be permitted, I would like to emphasize the great service which he, under Col. Bushnell, rendered to our army and therefore to our country. In the opportunities which I have had with General Gorgas in visiting our camps, it has

been the greatest satisfaction to find that there was always a first class medical man at the head of the medical service in the camp hospitals. These physicians and their staffs were selected for this service by Dr. Janeway. He often had to persuade some doctor, usually a successful and active practitioner of the right age for this service, that his duty was to give up his practice and to enter the army for this work. It is a great satisfaction to all of his friends to feel, as has been so well expressed by the Surgeon General, that he was able to render this great service to his country. He felt intensely about the war and was glad that he had an opportunity to serve. He would not have done differently if he had foreseen all that was to come. I think we may say he died as truly in the service of his country as if he had fallen in battle.

DR. JOHN HALL: SHAKESPEARE'S SON-IN-LAW[1]

By Eli Moschcowitz, A. B., M. D.

The physician whose story I propose to tell you to-night was not born great; he did not achieve greatness; he had greatness thrust upon him. He blazed no trail in medicine; nor, like some of our calling who were not even great as doctors, did he distinguish himself in the sister sciences, the arts, the pursuit of the Muses, or the love of his fellow-men. He was just an ordinary general practitioner. He little dreamed, on the day he took Shakespeare's daughter as his bride, that he was rescuing himself from a deserved oblivion.

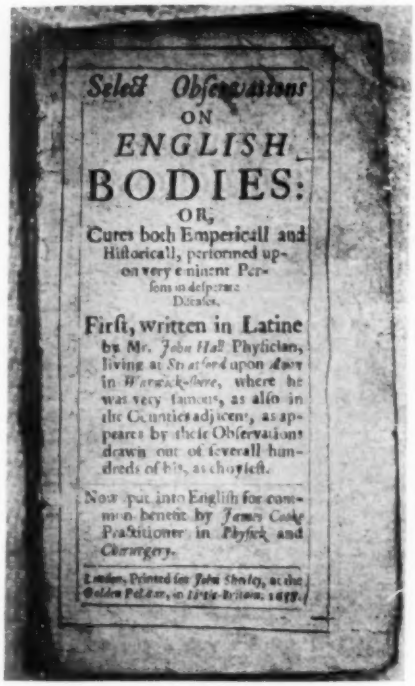
What then is the purpose of celebrating a person of such slender pretensions to fame? Even the pride we naturally feel that the son-in-law of Shakespeare was a physician would not suffice to commemorate John Hall. It so happens, however, that he wrote a book of case reports gleaned from his own practice, which, medically speaking, is of no value, but yet is of interest to us because it affords a fair record of the state of medical practice in his day. But above all it has an intenser and wider interest, because, avid as we are for every fact, no matter how trivial, that brings us into contact with Shakespeare, this book draws us into a close acquaintance with Shakespeare's family and social circle. And so to-night instead of ranging the Mounts of Olympus, we shall nestle, for a fleeting moment, by the fireside of William Shakespeare.

The direct stimulus to this study was the opportunity to peruse the rare volume written by John Hall and published for the first time in 1657.[2] It is duodecimo, and bears the following inscription on the fly leaf (Fig. 1): "Select observations on English Bodies; or, cures both empericall and historicall, performed upon very eminent persons in desperate diseases. First, written in Latine by Mr. John Hall, Physician, living in Stratford upon Avon in Warwick-shire, where he was very famous, as also in the counties adjacent, as appears by these observations drawn out of severall hundreds of his, as choysist. Now put into English for common benefit by James Cooke, Practitioner in Physick, and Chirurgery. London, printed for John Sherley, at Golden Pelican, in Little Brittain, 1657."

John Hall, who married Shakespeare's eldest daughter, Susanna, in her 25th year at Stratford on June 5, 1607, was born in 1575, and although he was a master of arts, he never attained a medical degree. How he obtained his medical knowledge is not known. In his youth, as usual at that time with people of means, he traveled on the continent. Just when he arrived at Stratford is not known; the first notice of any record of him is his marriage to Susanna, so that it is quite probable that he settled in Stratford only after his marriage. The only other records of Hall during Shakespeare's lifetime, is one in 1611, when his name is found in the list of supporters to a highway bill, and one in 1612, when he leased a small piece of woodland on the outskirts of the town. The Halls lived in a house in the thoroughfare leading to the church in a part of Stratford known as the Old Town. The house is still standing (Fig. 2) and bears the name of Hall's Croft. At all events, here he acquired an extensive practice and bore a considerable local reputation as a skilled physician, as shown by the fact, recorded in his book, that he was often called to treat the Earl or Countess of Northampton, 40 miles away. Dr. Hall apparently was a person of importance in the town of Stratford, for in 1617 and in 1623 he was elected a burgess, but for unknown reasons he was excused from undertaking office. In 1632, he was again elected and accepted the office. He quarreled with his associates concerning the matter of fines for non-attendance and other matters, and in October, 1633, he was expelled after the following resolution had been passed: "At this Hall, Mr. John Hall is displaced from being a Capitall Burgesse by the Voices and Consent of Nineteene of the Company, as appeared by the letter r at there names, for the breech of orders wilfully, and sundry other misdemeanors contrary to the duty of Burgesse and the oath which he hath taken in this place, and for his continual disturbance at our Halles, as will appear by the particulars." That he was a man of strong passions is also shown by the Linacre professor who translated his book from Latin into English for Dr. Cooke, and who says of him in the preface that "Such as hated him made use of him." The professor probably refers especially to Hall's deep religious convictions. He was an avowed Protestant with puritanical leanings, which became more pronounced as he grew older. Indeed, it is upon Hall, who was executor and, with his wife, residuary legatee of Shakespeare's will, that most of the blame is laid for the loss of Shakespeare's manuscripts of his plays.

[1] Read before the Historical Section of the New York Academy of Medicine, October, 1917.

[2] I am indebted to the Walpole Galleries of New York City for this privilege, for which I thank them.



Select Observations
ON
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BODIES:
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Cures both Empericall and Hiſtoricall, performed upon very eminent Perſons in deſperate Diſeaſes.
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London, Printed for John Sheiley, at the Golden Pelican, in Little Britain. 1657.

FIG. 1.

FIG. 2.

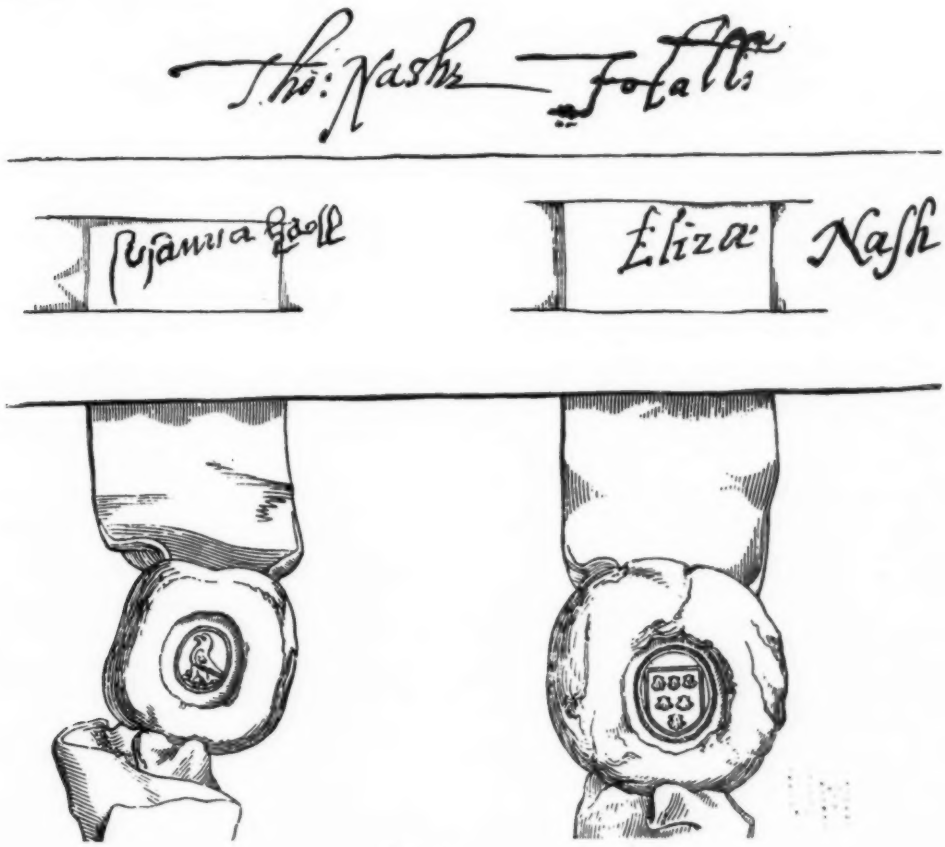

FIG. 3.

He died November 25, 1635, and was buried in the parish churchyard. His tombstone records the following inscription: Here lyeth ye Body of John Halle gent. He marr. Susanna daugh. (co-heire) of Will. Shakespare gent. Hee deceased Nove. 25, A: 1635. Aged 60.

Hallius hic situs est, medica celeberrimus arte:
Expectans regni gaudia laeta Dei;
Dignus erat meritis qui Nestora vinceret annis,
In terris omnes sed rapit aequa dies.
Ne tumulo quid desit, adest fidissima conjux,
Et vitae comitem nunc quoq; mortis habet

Hall's book, which reports 200 cases, was written in Latin. The manner in which the book was published is interesting and reveals a human touch so Boswellian, that nothing that we know of Shakespeare himself approaches it in intimacy. In 1642, during the Civil Wars, Surgeon Cooke, on duty with a regiment guarding a bridge over the Avon, was acquainted by a friend that Mrs. Hall had some books and manuscripts which her husband had left behind him.[3] He visited her at New Place and, "after a view of them Mrs. Hall told me she had some books left by one that professed physic with her husband for some money. I told her, if I liked them I would give her the money again; she brought them forth, amongst which there was this [referring to the book] with another of the authors both intended for the press. I being acquainted with Mr. Hall's hand, told her that one or two of them were her husbands and showed them her; she denied, I affirmed, till I perceived she began to be offended; at last I returned her the money." This shows, first, that Susanna apparently inherited some of the business acumen of her father. It also reveals that she cared more for money than for books. It also shows that either her education was not sufficient to enable her to detect her own husband's handwriting (her own signature (Fig. 3) reveals anything but a practiced hand), or, that she did not want it to appear that she was willing to part with anything belonging to her husband, to whom, as we shall see, she was closely attached. At all events, Cooke took it to London to have it translated by the Linacre professor mentioned above.

The book evidently had a reasonable popularity, probably as a household manual, for it went into two editions, in 1679 and 1683. Certainly the appeal to the general public must have been very strong, for all the 200 case reports are cures.

From the contents of the book, I gather that Dr. Hall was a general practitioner, with little or no leanings to surgery. His patients cover a wide social range, including lords, earls, baronets, countesses, squires, Catholicks, goodwives, gentlemen, barbers, maids, household servants and children. The earliest case report of which any date is furnished is that of Lord Compton, who was attended previously to his lordship's departure to Scotland with the king in 1617.

Medically speaking, as I have said, the book is of no value. Dr. Hall was probably no worse and probably a little better than the average country practitioner of his time. The book does not bear evidence of having been written for the eye of the medical fraternity, so that he had little occasion to reveal the depths of his learning. There is no clinical observation, diagnoses are paraphrased into colloquial parlance, the precision of diagnosis seems intended to impress infallibility;—all in all, the case reports are merely the barest outlines and serve as delicate frameworks upon which to hang the elaborate and inevitable cure. The materia medica employed by Hall is extensive, consisting largely of the Galenical plants, with occasionally such mediæval remedies as the dried windpipe of a cock and the dung of various animals. It mirrors largely the therapeutical combination of superstition and empiricism of his time.

The diseases cured by Hall are of the most diverse sort. We may well envy Dr. Hall, who cures by the simplest means diseases in which we, the possessors of a heritage of centuries of the most brilliant discoveries, feel nearly helpless. Thus he reports many cures of dropsy, the falling sickness, melancholy, sterility, enuresis, cancer, etc. Be that as it may, the diseases mentioned in Hall's book cover a wide range. Gynecological diseases are common; postpartum sepsis, sterility, "the whites," dysmenorrhea and menorrhagias. Scurvy seems to have been especially common; also round worms. In addition we find various fevers, including "Enterick" and "Tertian," constipation and other intestinal disorders, especially "the colick," respiratory disorders, gonorrhea, etc.

Commentators have speculated freely upon where Shakespeare derived his amazing knowledge of medicine. I venture to suggest that Shakespeare was indebted largely to Dr. Hall. Certainly he knew his son-in-law for at least nine years, and perhaps longer, before he died, and probably they were no more averse to discussing professional matters with one another, than men in the same professions are to-day. Another leading circumstance, is the fact, as Dr. M. Kahn of this city pointed out to me, that most of Shakespeare's knowledge of things medical is displayed in his tragedies, most of which were written in the later years of his life.

And now we come to the more passionate interest that this book bears. Had Dr. Hall written nothing but the case reports of obscure persons, the book to-day would have been only a curiosity, the mere prey of the collector of Shakesperiana. Fate has so ordained, however, that Dr. Hall happened to include among his case reports the illnesses of persons known to the immortal William himself, so that with another stroke of luck, Hall raises himself from the position of an obscure relative of Shakespeare to the dignity of an historian.

[3] **The will of John Hall. "The Last Will and Testament noncupative of John Hall of Stratford-upon-Avon in the county of Warwick, gentleman, made and declared the five and twentieth of November 1635. Imprimis, I give unto my wife my house in London. Item, I give unto my daughter Nash, my house in Acton. Item, I give unto my daughter Nash, my meadowe. Item, I give my goodes and money unto my wife and my daughter Nash to be equally divided betwixt them. Item,—concerning my study of books, I leave them, sayd he, to you, my son Nash, to dispose of them as you see good. As to my manuscripts, I would have given them to Mr. Boles, if he had been here, but inasmuch as he is not heere present, you may, son Nash, burne them, or doe with them what you please. Witness, thereunto, Thomas Nash, Simon Trapp."**

Some were relatives, many were his close friends. Thus we find two references to his daughter Susanna, Hall's wife; Hall's only daughter, Elizabeth, Shakespeare's granddaughter, upon whose death in 1670 Shakespeare's direct lineage ceased; Hall's own sickness is recounted. Also that of Michael Drayton, the poet, with whom Shakespeare and Ben Jonson, according to Vicar Ward's testimony, "had a merrie meeting, but Shakespeare seems drank too hard, for he died of a fever there contracted." This is the only scrap of information we possess of the manner of Shakespeare's death. Indeed, it is not a great stretch of fancy to think that Dr. Hall may have attended Shakespeare during his last illness, and had Hall been as willing to risk his failures as his cures for publication, we might have found Shakespeare's last illness recorded here. We also find the case of Mr. Queeny who was, undoubtedly, that Richard Quiney who died in 1602, and after whose wife Shakespeare's eldest daughter Susanna was named. He was a mercer, and bears the distinction of being the author of the only extant letter to Shakespeare, in which he appealed for a loan of money in 1598. His son, Thomas Quiney, married Shakespeare's second daughter Judith. Mrs. Sadler (p. 13) must have been Judith Sadler after whom Shakespeare's second daughter was named. Hamnet Sadler's name was given to Shakespeare's only son. Hamnet Sadler was an intimate friend and one of the beneficiaries under Shakespeare's will. Anne Ward (p. 212) may have been related to the Vicar of Stratford to whom we are indebted for the only account of Shakespeare's death. A Captain Bassett, who is mentioned twice, may have been the original of the character of that name found in King Henry VI, Part 1.

The following case reports, which have been selected either for their human or their medical interest, serve to indicate the character of Dr. Hall's book:

"Obs. 19. Mrs. Hall of Stratford my wife, being miserably tormented with the colick, was cured as followeth; ℞ Diaphaen. Diacatholic. ana ʒi; Lact. q. s. f. Clyst. This injected gave two stools, yet the pain continued, being but little mitigated, therefore I appointed to inject a pint of sack made hot, this presently brought forth a great deale of wind, and freed her from all pain, to her stomach was applyed a plaster de Labd. Cret. cum Canan. et Spec. Aromat. rosat. et Ol. Macis. With one of these glysters I delivered the Earle of Northampton from a grievous colick.

Obs. 36. Elizabeth Hall, my onely daughter was vexed with totura oris or the convulsion of the mouth, and was happily cured as followeth. First I exhibited these pills; ℞ Pil. Coch. et Aureas, ana ʒi; f. pil. 10. She took five the first day which gave her seven stooles. I fomented the part with Theriac. Androniac. and Aq. Vitae. To her neck was used this, ℞. Lingu. Martiat. Magn. ʒi; Ol. Laverin. petrolei, Castor. et Terebinth. ana ʒiss de lateribus ʒi; misce. by this she had great advantage, her courses being obstructed, thus I purged her. ℞. Pil. foetid. ʒi Castor ʒi; de Succin. rhab. egaric. ana ℈i; f. Mass. she took five pills in the morning," etc.

The account of Elizabeth is extremely long, so I shall abbreviate the remainder. On January 5, 1624, she had an ophthalmia. In April she went to London; on the 22d she returned home. She took cold and "fell into the said distemper on the contrary side of her face." On May 24 she was attacked by "enterick" fever, which he also duly cured.

I have summarized the report of his own illness, because in the original, it is too long. Pious man that he was, he prefaces his account with a prayer.

Obs. 60. (2) "Thou O Lord who has the power of life and death, and drawest from the fates of death, I confesse without any art or counsell of Man, but only from thy goodnesse and clemency; Thou has saved me from the bitter and deadly symptoms of a deadly fever, beyond the expectation of all about me, restoring me as it were from the very jaws of death to former health, for which I praise thy name, O most merciful God, and Father of Our Lord Jesus Christ, praying Thee to give me a most thankfull heart for this great favor, for which I have cause to admire Thee."

On August 27, 1632, in the 57th year of his age, he had an attack of severe hemorrhoids. He was constipated 14 days; nevertheless, he says, that he "was constrained to visit many of his patients." A fever followed. He first purged with rhubarb. A delirium set in, which was cured by "opening a live pidgeon and applyed to his feet to draw down the vapors." At this part of his illness, his wife became alarmed, so two physicians were called into consultation who again purged him fully, and prescribed a formidable host of drugs. In the meantime, "ℨ vii of blood was drawn from the liver veine and leeches were applyed to the haemorrhoids." During the convalescence he took Chalybeate Wine as a tonic, and was troubled with a scrotal itch which was cured with a "decoction of sarsparilla with antiskorbutick herbs."

"Obs. 22. Mr. Drayton an excellent Poet, labouring of a Tertian was cured by the following ℞. The Emetick infusion; Syrup of violets a spoonful, mix them; this given, wrought very well both upwards and downwards."

Obs. 38. The report of Mr. Queeney's illness is distinguished by the fact that a troublesome cough was treated with a gunshot prescription containing 28 ingredients. This apparently proved ineffectual, for soon after Dr. Hall ordered his head to be shaved and in addition prescribed four additional prescriptions. Then follows the only report of a fatality throughout the book. "Being not wholly freed from it, he fell into it again next year, all remedies proving successless, he dyed. He was a good wit, expert in tongues and very learned."

I shall cite only a few of the case reports that are of unusual medical interest. Gynecologists may be interested in the three following cases:

"Obs. 52. Mrs. Sheldon, wife to the son, being corpulent, well coloured, was wont to miscarry often, the second month after conception, yet suffered no other accident with it, required my counsel, I advised her to purge, and strengthen the womb, for which she took sage in her drinks and meats, also a little of the following in a raw egg. ℞ Gran. tinctor. Marjorit. tormentili ana ʒi; Mastic. ʒiss misc. f. pil. there was given as much as would lie on a groat. For the retaining the infant, this is the best plaster. ℞ Labd. puris. ʒiss Gallar. Mirtel. Ros. Rub. Sang. Dracon. balanst. ana ʒ iss pil. Naval. ʒ ii Tereb. ʒ vi Malax. omnia simul, f. Empl. part of which spread on leather, and applyed to the loynes, os sacrum, and the bottome of the Belly. This she used all her time, and after brought forth a lusty hearty son, and after that more."

"Obs. 26. Mrs. Broughton of Causon, aged 28. Three days after miscarriage in the fifth moneth fell into a fever accompanied with abundance of after-fluxes, vomiting, loathing, thirst, swoon-

ing, and in danger of death was speedely helpt as followeth. ℞ burnt Hartshorn finely powdered ʒ i; boyl it in three quarts of Spring water till a quart be wasted, then remove it from the fire, after adde syrup of Lemons ʒ ii; rose water ʒ iv, sugar a sufficient quantity. This she drank constantly instead of drink, which gave great ease. The following decoction was given morning and evening, which did clense, cure, cast out, and extinguish thirst. ℞ French barley m iv violets P ii, liquiris ʒ iss, jujebs ʒ i; Sebestens ʒ ii; carduus benedictus m iss; make a decoction in sufficient quantity of water to ℔ xii to the straining, adde sugar of violets and make a drink. By these medicines alone she was cured beyond all expectation."

"Obs. 47. (second series). My Lady Rainsford, beautiful and of a gallant structure of body, near 27, was three days after her being laid of her child, miserably tormented with pain in her belly, from which I delivered with the following. ℞ the white of Hens Dung ʒ i; being put in beer and sugar, she took it. To the belly the following was applyed hot. ℞ New milk and Honey, each ℔ i horehound m i; wheat flour ʒ iii, seffron; ʒ i; boyl them to a pultis. By these she was delivered."

The following reports are of pediatric interest:

"Obs. 35. A child of Mr. Walkers of Ilmington, minister, aged six moneths afflicted with falling-sickness, by consent was thus freed. First, I caused round pieces of piony root to be hanged about the neck, when the fit afflicted I commanded to be applyed with a spunge to the nostrils the juyce of Rue mixt with White Wine Vinegar, by the use of which it was presently recovered, and falling into the fit again, it was removed in the same manner. To the region of the heart was applyed the following. ℞ Theriac. Ver. ʒ ii Rad. palon. pul. ʒ ss misc. The haire was powdered with powder of the roots of pioney and thus the child was delivered from all its fits."

Here is a case that Dr. Cullen might introduce into the next edition of his monumental work on Diseases of the Umbilicus:

"Obs. 98. Dixwell Brunt of Pillerton, aged 3, had a tumor of the navil, out of which broake five long wormes out of a little hole, like a fistula; the nurse pull out four dead, but the fifth was somewhat alive; the forepart moveing, the hinder part stirred, as witnessed the nurse, Father, Mother and Maide; the tumor being hard, I appoynted a plaster of hony to be applyed, but no wormes appeared; the next day was applyed a Cataplasme of green Wormwood, beat with the gall of an oxe, and boyled. There was given a suppository. After these the navil was cured and he lived.

"Obs. 60. Talbot the first born of the Countess of Salisbury, aged about one yeare, being miserably afflicted with a fever and wormes, so that death was onely expected, was thus cured. There was first injected a glyster of milk and sugar, this gave two stooles, and brought away four wormes. By the mouth was given Hartshorn burnt, prepared in the farme of a julep. To the pulse was applyed, Ungu. Papuleon ʒ ii; mixt with spider's webs and a little powder of nut shells. It was put to one pulse of one wrist one day and to the other the next. To the stomach was applyed Mithridate, to the navel the Emplaster against wormes. And thus he became well in three days, for which the Countess returned me many thanks, and gave me a great reward."

Hall was not bound too rigidly by the rules of professional secrecy as the report of the following case reveals. Here is how Hall cures a gonorrhea:

"Obs. 80. William Clavel troubled with a virulent gonnorrhea and extreme heat of urine, having been under anothers hands for a moneth without profit was cured with the following remedyes in fifteen days space, being in the moneth of November. ℞ Gum Guaiac pul ʒ i; it was given in beer, it gave five stooles. Afterwards he took a pint of the following decoction morning and night. ℞ Sarsp. ʒ ii; Hermodactyles ʒ iss; Guaiacum, Liquiris, each ʒ i; Seny ʒ i; Seeds of Anis Carraway and Cariander, each ʒ ss; boyl them in eight pints of water till half be wasted. After the strained liquor was taken, there was given the following electuary. ℞ Gum Tragacanth ʒ ss; dissolve it in sufficient quantity of plantain water, strain it, adde gum Guaiacium powdered ʒ ii; Terebinth burnt ʒ i, mix them. Dos. ʒ iss; By the use of the decoction of Sarsa. he was very well purged, and delivered altogether from pain in the loynes and heat of the urine in four dayes, and by the use of the electuary he was altogether cured of his gonnorrhea."

It now only remains, as in the last chapter of a novel, to relate the fate of some of the characters that have passed before our gaze. There is a melancholy interest in this telling, because we find that all of Shakespeare's descendants died before the end of the seventeenth century, so that the most prodigious and universal mind the world has ever known had but a brief blossoming. You may remember that Shakespeare and Anne Hathaway had three children; a son, Hamnet, and two daughters, the younger Judith, the elder Susanna. Hamnet died in his 12th year during the poet's lifetime in 1596. Judith married some two months before the father's death, Thomas Quiney, son of the Richard Quiney mentioned in Dr. Hall's book. The bride was 32 years old; her husband was her junior by four years. Thomas Quiney was a vintner, and became a chamberlain and a burgess of Stratford. He became involved in much litigation, had financial reverses and moved to London, where, apparently, he died in poverty. The Quineys had three sons, Shakespeare who died in infancy, and Richard and Thomas, who both died soon after reaching manhood. As neither of the latter had issue, the line of the poet in this direction became extinct in 1662 when their mother, aged 77, died.

Of Susanna, Dr. Hall's wife, we know little except that in 1613, during Shakespeare's lifetime, she brought a suit for defamation of character against a John Lane, Jr., who had circulated a libelous rumor of immoral conduct. The slanderer, however, failed to appear, and a sentence of excommunication was passed against him. She died July 11, 1649, and her tombstone is marked with the following verse:

"Witty above her sexe, but that's not all,
Wise to Salvation was good Mistress Hall,
Something of Shakespere was in that, but this
Wholy of him with whom she's now in blisse.
Then, passenger, ha'st ne're a teare,
To weepe with her that wept with all?
That wept, yet set herselfe to chere
Them up with comforts cordiall.
Her Love shall live, her mercy spread,
When thou hast ne're a teare to shed."

The Halls' only child, Elizabeth, was nine year old when her grandfather died. She married in Stratford in 1626, Thomas Nash, a Stratford resident of considerable property. Born in 1593, he was a student at Lincoln's Inn. His father and uncle were intimate friends of Shakespeare. Mrs. Nash became a widow in 1647, and two years later married John Barnard, a

gentleman of wealth. Having no issue by either husband, the last descendant of William Shakespeare died in 1670; and so, like an organ peal in the dusk, the lines of her immortal grandfather's first sonnet serve as a fitting close:

"From fairest creatures we desire increase,
That thereby beauty's rose might never die,
But as the riper should by time decrease
His tender heir might bear his memory;
But thou, contracted to thine own bright eyes,
Feeds't thy light's flame with self-substantial fuel,
Making a famine where abundance lies,
Thyself thy foe, to thy sweet self too cruel.
Thou that are now the world's fresh ornament
And only herald to the gaudy spring,
Within thine own bud buriest thy content
And, tender churl, makest waste in niggarding;
Pity the world, or else this glutton be,
To eat the world's due, by the grave and thee."

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PROCEEDINGS OF SOCIETIES

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY

JANUARY 7, 1918

1. Demonstration of a Duodenectomized Dog. (Abstract.) DR. ERNEST G. GRAY.

In the course of some experiments having to do with the effects of the diversion of the pancreatic juice into the stomach upon the level of gastric acidity it became desirable to extirpate the duodenum. A review of the literature, however, disclosed no record of a successful duodenectomy. This portion of the intestinal tract was first removed by Minkowski, but as his experiments and those of subsequent workers only covered a period of a few weeks no evidence exists concerning the ultimate effects of such an extirpation. The principal reason, probably, why it has been impossible to keep animals living for any considerable length of time following this operation, is that the endeavors to re-establish a channel of communication between the pancreas and the intestinal tract have all been without result.

A new problem then presented itself, the question as to whether the surgical difficulties encountered in the course of the excision of the duodenum might be successfully met. It is the results of some work bearing on this subject to which I wish to refer tonight.

Experiments dealing with this problem were started about a year ago. Of a series of dogs used for this purpose one animal survived the various operative procedures, some died of pneumonia, others of distemper, etc. The extirpation was carried out in three stages. At the first operation the gall-bladder was anastomosed to the proximal jejunum and the common bile duct doubly ligated and divided. Some time subsequent to this the major pancreatic duct was dissected from the duodenal wall and transplanted into the jejunum a short distance from the site of the cholecystenterostomy opening. Then in a third stage the entire duodenum was extirpated and end-to-end anastomosis made between the antrum of the stomach and the proximal jejunum. In order to preserve the vascular supply of the pancreas a very narrow strip of the muscular coat of the duodenum (on the side of the bowel facing the pancreas) was left attached to the pancreatico-duodenal vessels. The margins of this layer of muscle cells were then crushed and stitched together to control bleeding.

The duodenum was removed from the dog which you see before you eight and one-half months ago. Each of the three abdominal wounds healed per primam. Since the resection the animal has gained about 6 ounces in weight (a small fox terrier), his appetite being rather above that of a normal dog. Repeated tests have never revealed the existence of any glycosuria. The stools have been normal in appearance. Throughout the past eight months the dog has continued in excellent health and has always been as active as he appears tonight.

The results of the experimental work just outlined demonstrate conclusively, first, that a dog may remain in good health following a total duodenectomy, and second, that the pancreas may be successfully connected with the intestinal tract after the removal of the entire duodenum.

2. The Origin of the Corpus Luteum. DR. G. W. CORNER, San Francisco, Calif.

3. On the Absorption of Drugs and Poisons from the Vagina. (Abstract.) DR. DAVID I. MACHT.

While a large number of drugs are introduced into the vagina in the form of douches, tampons, suppositories, "uterine wafers," etc., and while a search in clinical literature reveals undoubted cases of poisoning occurring through this channel, no experimental work except that of a clinical character is on record on the subject. In connection with the study of the question of absorption of drugs through unusual channels, the author undertook a systematic study concerning absorption of drugs and poisons from the vagina. A large number of drugs were investigated in this connection: Alkaloids, esters, antiseptics, and dissociable salts. As a criterion or proof of absorption, both physiological and chemical evidence was obtained. It was found that drugs of all kinds are absorbed surprisingly rapidly from the vagina. Thus, for instance, a few milligrams of apomorphin or morphin introduced into the vagina of a dog produced vomiting within five minutes. Among the alkaloids studied were: Morphin, apomorphin, pilocarpine, atropine, cocaine and aconitin. Undoubted proof of absorption of various salts was given by experiments with potassium iodide, potassium ferrocyanide and potassium cyanide. Nitroglycerine is rapidly absorbed from the vagina; so

also are the nitrites of sodium and potassium. Of the antiseptics studied the chief ones were phenol, cresol and corrosive sublimate. All these were found to be very rapidly absorbed as evidenced by physiological and toxicological symptoms and also by chemical tests. The full paper on the subject appears in the *Journal of Pharmacology and Experimental Therapeutics*, Volume X, page 509, January, 1918. In the paper, in addition to the experimental data, an exhaustive review of the clinical evidence is appended and the conclusions reached are as follows:

1. That all kinds of drugs and poisons—alkaloids, inorganic salts, esters and antiseptics—can and are easily absorbed through the vaginal wall.

2. Such absorption is demonstrable by physiological and chemical means.

3. A review of the clinical and toxicological literature shows that poisoning through the vagina of a grave character is not at all uncommon.

4. The experiments reported indicate on the one hand the possibility of rational administration of drugs for therapeutic purposes through the vaginal route; and, on the other hand, emphasize the great danger of indiscriminate employment of various substances in the form of douches, tampons, "uterine wafers," etc.

3a. On the Absorption of Drugs from the Urethra, Bladder, Ureters and Pelvis of the Kidney. (Abstract.) DR. DAVID I. MACHT.

Following the report on absorption from the vagina, the author reports studies on absorption from the various parts of the urinary tract. A large number of drugs were studied in this connection. The results may be briefly summarized as follows:

Absorption of drugs from the urethra is very rapid. The posterior urethra, as compared with the anterior one, absorbs more rapidly. As compared with the whole urethra, the absorptive powers of the bladder are surprisingly poor. Thus, for instance, while apomorphin in a dog is rapidly absorbed from the urethra producing vomiting in a few minutes, the same amount and even larger doses of the drug, when introduced into the bladder and prevented from being regurgitated into the urethral canal, produce vomiting after a much longer period of time (half an hour or longer) and sometimes not at all. Among the drugs studied were: Various alkaloids such as morphin, apomorphin, atropin, cocaine, aconitin, pilocarpine, etc.; various salts such as potassium cyanide; and antiseptics such as phenol, resorcin, cresol, etc. Absolute proof is furnished by further experiments that alkaloids and other drugs can be absorbed through the ureters; and some experiments indicate also that absorption may take place from the pelvis of the kidney. The full report of this investigation will be published in several installments in the *Journal of Urology*.

JANUARY 21, 1918

1. Cinq ans Après. DR. F. C. SHATTUCK, Boston, Mass.

This article appeared in the April number of the BULLETIN.

2. Exhibition of a Case of Internal Hydrocephalus. DR. W. E. DANDY.

This child is presented to the Society because we have reason to believe that it is a case of internal hydrocephalus that has been cured by operation. This statement of course must be accompanied by considerable reservation. Only time will tell whether the result is permanent. We believe the child to be cured: First, because of the tests which Dr. Blackfan and I have been using, and second, on account of the symptomatic improvement that has taken place since operation.

The child came in about three months ago with what proved to be internal hydrocephalus of the obstructive variety. Since this time, the improvement we have been able to note has been one of moving the head from side to side. On admission, the head was a dead weight; he was unable to move it more than a few millimeters. He is now able to hold the head up to a slight extent.

You probably know from the work Dr. Blackfan and I have been doing that there are two types of internal hydrocephalus which can be absolutely differentiated by the phenolsulphonephthalein test. They are both physiologically similar because both are due to cerebrospinal absorption. In the one type the obstruction is in the intraventricular system; in the other, it is in the subarachnoid space.

This was a case of the obstructive type, and it is only this type which offers any hope of relief by this procedure. The other type may be amenable to treatment, but in an entirely different manner. This is the first case we have had an opportunity to follow and see the results. The operation consisted in the usual cerebellar approach with removal of the occipital bone. We knew from the test that the obstruction was either at the aqueduct of Sylvius or at the basal foramina of Magendie and Luschka. We could not tell at which point until operation.

In one other previous case, we tried to catheterize the aqueduct of Sylvius to relieve obstruction by passing a sound through the aqueduct, being guided only by the sense of touch after passing through the foramen of Magendie. In this case we split the cerebellum and the roof of the fourth ventricle and could see the aqueduct of Sylvius, so that we knew exactly where we were passing our sound. We passed a small catheter through the aqueduct and released an obstruction which was little more than a film. To keep the obstruction open, a tube was introduced. Exactly how to maintain the open aqueduct was a problem. For this purpose, we had to use other surgical observations. Our plan of attack was quite analogous to the line of the procedure against obstruction of the common bile duct. We left the tube in about three weeks. The procedure was accompanied by a fairly severe reaction. Of course we did not know how long the tube should remain in the aqueduct. We were only able to judge by observing the child and its ability to stand reaction. The fontanelles became tense and the child vomited more or less persistently and increasingly. At the end of the three weeks, we decided we should not wait any longer and removed the tube. The symptoms immediately disappeared. That has been nearly a month

ago. We tested the patency of the aqueduct yesterday and found that fluid introduced into the ventricle passes freely into the subarachnoid space. Consequently, we have every reason to believe that the case so far is cured. That is, the ventricles communicate, and it was their failure to do this which caused hydrocephalus in the beginning.

3. Visits to Cantonments. (Abstract). DR. WELCH.

It may be worth while to say a few words about some of my experiences of the last few weeks, during which I have had the opportunity of visiting various cantonments. My first visit was in behalf of the Public Health Service to see the work Dr. Goldbacher and his staff had been conducting on pellagra. They have done a splendid piece of work on this very perplexing subject. In my opinion Dr. Goldbacher has shown that the disease is entirely controllable and preventable, both as regards fresh attacks and recurrences.

I was then asked to visit various camps, covering a good deal of territory. The mode of procedure was usually to first pay a call upon the general in command and then upon the division surgeon. Our time was spent with him in inspection of the camp, the infirmaries and in gathering statistics as to the incidence of disease. A good deal of time was also spent in sanitary inspection, and at the base hospital.

As regards the medical organization of the camps, the medical officer in command of the medical service is the division surgeon, who is always a regular army man, a member of the regular army medical corps. It would take very little experience to convince one that no man taken from civil life could possibly fill this position. While professional qualification is fundamental, a man must be a soldier to be a good military medical officer, and the military side of it is just as important as the other. The division surgeons are of the greatest importance and almost without exception they are men of real capacity and fill the positions ably. There is always an aid or assistant to the military surgeon. He is sometimes a medical man, and more frequently also of the regular army.

Then comes the sanitary inspector, who is a very important official. He may be either a member of the regular medical corps, or a member of the reserve corps.

In the base hospitals there is of course the director of the hospital, who is usually a regular army man. His work is mainly administrative. This is quite an important position and is pretty ably filled as a rule. Under the director of the hospital there are the chief of the medical service and the chief of the surgical service. I may say here that any one who has had an opportunity of seeing this organization will realize that Dr. Janeway has done a very great service to his country. At every one of these hospitals there is an unusually good man. That was Dr. Janeway's work in the surgeon general's office, to make sure that there was at least one capable, energetic and enthusiastic young medical man taken from civil life for the purpose of assuming this responsible office. When you see such men as we found in the base hospitals, doing such good work, you are filled with admiration for the work which Dr. Janeway did. As I say, there is in almost every case a good medical man, and he considers himself fortunate if he can get at least five younger men to look after hearts and lungs, take histories and see to the patients in the wards. I may say that the question of qualifications for these very important positions is regarded as a very serious one in the surgeon general's office.

The older disease which we associated with camp life are no longer those which prevail. What we formerly regarded as the unsanitary condition of camps related to environment, water supply, etc. Today a new group of diseases has taken the place of typhoid fever and dysentery. They are the acute respiratory infections, in which may be included measles and meningococcus infections, and they are conveyed directly or indirectly from person to person. The emphasis is no longer on the type of work done ordinarily by the sanitary inspector in looking after drainage, garbage, etc., important as this work is. All that does not touch these diseases which form a new chapter in military hygiene, a chapter which is divided into two parts: In the first place, more accurate studies of the subject; and in the second, skilled epidemiologists in our camps. It has been arranged that all this work shall be carried out.

FEBRUARY 4, 1918

1. A New Hypophysis Operation. Devised by DR. G. J. HEUER. (Presented by Dr. W. E. Dandy, in Dr. Heuer's Absence.)

When Dr. Heuer was suddenly called to France last summer, he was prevented from publishing this operation and its presentation will no doubt be deferred until the close of the war. With this in mind, Dr. Halsted thought that priority should no longer be risked, and suggested that I present the salient features of the operation before this Society.

As you know, numerous operations have been devised for hypophyseal tumors: McArthur's and Frazier's through the roof of the cranium; Dr. Cushing's removal of the floor of the sella turcica; and various others. None of them, however, are really more than an *approach* to the hypophysis; that is, after the gland has been exposed, the operator has had to desist without attempting to remove the tumor. At most, only a fragment could be removed, and this, only sufficient to make a diagnosis, offered no therapeutic benefit to the patient. Dr. Heuer's operation really opens up a new field for hypophyseal tumors. Up to this time none of the operations have given any way of successfully removing a hypophyseal tumor. The exposure was too limited and nothing could be accomplished except in a very few cases in which a cyst was present which could be punctured.

By this new operation, it is possible to thoroughly expose the hypophyseal region, to expose the tumor and to determine whether it is or is not enucleable. If the former, it can be removed by this method. We have employed this mode of procedure in about 20 cases. I think the operation can best be demonstrated by means of a few slides which will be shown.

The first slide shows the outline of the incision. It consists of a very large bone flap carried well toward the supraorbital margin, with the base parallel to the zygoma. With a very

large bone flap turned down and the dura similarly incised, there is sufficient relief of pressure from an intracranial tumor to allow approach to the hypophyseal region and give sufficient room for exploration.

The second slide shows a tumor protruding between the optic nerves at their point of entrance into the optic foramen.

The third slide shows a tumor removed, with the optic nerves intact. The tumor is shelled out in the space between the two optic nerves.

Hypophyseal tumors have been the most discouraging part of neurological surgery and until the advent of this operation it seemed almost useless to operate, because there was nothing one could do except in the rare instances of hypophyseal cyst. Now the prospects are very much brighter and we feel discouraged if we are not able to take out the tumor. Of course, there are various types of tumors and the differentiation can be made only by operation, but by operating one can absolutely decide whether or not it is possible to remove the tumor. This can be done in no other way except by this operation devised by Dr. Heuer.

2. **Observations upon the Pathology of Diabetes.** DR. FREDERICK M. ALLEN, Rockefeller Institute for Medical Research.

3. **Results of Past Methods and To-Day's Problems in the Treatment of Diabetes.** DR. ELLIOTT P. JOSLIN, Boston, Mass.

This article appeared in the April number of the BULLETIN.

THE JOHNS HOPKINS HOSPITAL HISTORICAL CLUB

JANUARY 14, 1918

1. **The Historical Section of the Royal Society of Medicine in London.** Extract from Dr. Futcher's Letter to Dr. Hurd, December 16, 1917.

I am glad to know that the Medical and Historical Societies are still "carrying on."

Sir William Osler lets me know the dates of the meetings of the Historical Section of the Royal Society of Medicine, at their fine new building at 1 Wimpole Street, and I have been up twice. The meetings are at 5 o'clock, and as the Englishman can't get along without his afternoon tea, tea is always served before the meeting at 4.30. At the October meeting I met Colonel Adami, who is connected with the D. M. S. Office, Col. Darcy Power, Dr. Norman Moore, Professor Cushney, and others. This meeting was given over to Boerhaave. Sir William read the first paper—an excellent one—and showed the Boerhaave treasures, bought at Leyden when he made the pilgrimage there with Doctor Dock many years ago. The second paper was by a Leyden professor, but was read by the secretary, as the professor could not come. The perils of the North Sea are not conducive to travel at present. The last one was by Col. Darcy Power, and consisted of a translation of many of Boerhaave's letters to an English correspondent. Dr. Norman Moore entered into the discussion.

The November meeting was a joint one of the British Folklore Society and the Historical Society, and the paper was by the president of the former, an Oxford anthropologist. Title: "The Primitive Medicine Man." It was interesting, but as is often the case, Sir William's discussion was even more so.

Tom McCrae probably gave you a very good idea of the character of the work here. He left a splendid reputation behind him, as we would naturally expect. We are kept busy all the time. The 2080 beds are always practically all occupied. No sooner are evacuations made, than their places are taken by fresh convoys. Surgical cases predominate, but we always have from 600 to 900 medicals. The purely medical problems are largely those of a large hospital, although we have cases naturally not incidental to civil life, interesting perforating wounds of the chest, gassed cases, and trench fever, trench nephritis, etc.

The Russian collapse and the Italian retreat were very depressing. I am always hopeful, and if the French, Italians and British can hold their lines until the spring, I don't think for a moment that there will be any question of the ultimate outcome. The weight of the United States is bound to turn the scales, and all the editorial writers and military critics over here are most complimentary in their comments regarding the thorough way the United States has gone into the preparations for carrying on her share of the conflict.

The taking of Jerusalem has been a cheering bit of news. Its capture and that of Bagdad has helped to restore British prestige in the Mohammedan world. It had been badly shattered by the Gallipoli campaign.

Germany will make big efforts to break down the Allies before the United States can come in, but I think that a lot of what they say they are going to do is largely bluff.

I have had correspondence with Dr. Fayerweather, who is doing excellent work at a large orthopædic hospital at Leeds. I unfortunately missed seeing Dr. Young and Dr. Baer in London when they were there a few weeks ago. Being in the Imperial (Canadian) Service, I haven't the chance to meet as many of the Americans as I should like. Dr. Hall was down and spent a Sunday with us several weeks ago.

NEW PUBLICATIONS.

The following six monographs:

Free Thrombi and Ball-Thrombi in the Heart. By J. H. HEWITT, M. D. 82 pages. Price, $1.00.

Benzol as a Leucotoxin. By LAURENCE SELLING, M. D. 60 pages. Price, $1.00.

Primary Carcinoma of the Liver. By M. C. WINTERNITZ, M. D. 42 pages. Price, 75 cents.

The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL.D., F.S.S. 161 pages. Price, $2.00.

The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN. 94 pages. Price, $2.00.

The Nuclei Tuberis Laterales and the So-called Ganglion Opticum Basale. By EDWARD F. MALONE, M. D. Price, $1.50.

are now on sale by THE JOHNS HOPKINS PRESS, Baltimore. Other monographs will appear from time to time.

NOTES ON NEW BOOKS.

Burdett's Hospitals and Charities, 1917. Being the Year Book of Philanthropy and the Hospital Annual containing a review of the position and requirements and chapters on the management, revenue and cost of the charities, an exhaustive record of hospital work for the year, etc. Twenty-eighth year. By Sir Henry Burdett, K. C. B., K. C. V. O., etc. (*London: The Scientific Press, Limited, 28 & 29 Southampton St., Strand, W. C.*)

The somewhat tardy appearance of this annual volume is explained by the editor as due to difficulties incident to the war. We are promised that the volume for 1918 will be more promptly issued. We regret to see that Sir Henry Burdett speaks again of his desire to secure a competent person to relieve him of the labor which has borne heavily upon him for nearly 30 years. It is very doubtful whether any person can be found who has the same familiarity with the broader aspects of charity or an equal grasp of the practical details of hospital management. We trust that he may long continue to edit the work.

Probably the most interesting portion of the present volume is the chapter referring to hospital incomes and expenditures. The figures and facts presented show an unparalleled increase in the expenditures of all hospitals and corresponding increase of income. In many hospitals the income has doubled in the past 20 years, but outlay for supplies has more than kept pace with the increase of income. The increase of income has been derived from increased contributions on the part of the former contributors to hospitals, and also from grants from the government for the care of invalided officers and soldiers. The increase of expenditures is due to the higher cost of food, fuel, labor, medicines and supplies of every sort. Many articles of food have increased in price threefold, and of medicines and apparatus ten-fold. There have also been serious difficulties in the training of nurses for service abroad, and many increased expenditures due to the increase in the number of nurses required, and the cost of their supplies and equipment.

Another interesting chapter relates to the provision made for the care and training of those persons blinded in army service. It is most gratifying to read of the efforts made not only to care for the blind in their helplessness but also to fit them for self-support. It is not enough to make them comfortable. They must be made cheerful and self-respecting by instruction in trades and industries until they are capable of self-support wholly or in part.

Many old time topics are touched upon in the volume, such as the need of uniformity of accounts in institutions, the need of uniformity in training nurses, etc. The book is of great value, and should be in the hands of all hospital officers. We have nothing to compare with it in America. H. M. H.

Nutrition and Clinical Dietetics. By Herbert S. Carter, M. A., M. D.; Paul E. Howe, M. A., Ph. D., and Howard H. Mason, A. B., M. D. Cloth $5.50. (*Philadelphia and New York: Lea & Febiger, 1917.*)

This book furnishes a very welcome addition to the literature on nutrition and clinical dietetics. There is no branch of therapeutics which has been neglected more than diet. It has been only slowly realized that the administration of food, in disease or in health, is not a matter of common sense and intuition, but should depend upon an accurate knowledge of pathological physiology. Unfortunately, many of these underlying principles remain to be determined and consequently, when diets are ordered in the sick room, great discrimination and judgment are necessary.

Carter, Howe and Mason have produced an admirable volume. They have kept the scientific limitations of the subject in mind. Throughout they have furnished a very satisfactory and readable summary of the facts in each instance, and have based the diets advocated as far as possible on their conclusions. It is a pleasure to order diets under such directions.

Part I furnishes a simple yet forceful exposition of digestion, food requirements, normal feeding and food economics. The last is a particularly timely subject and is well, even if briefly, presented.

Part II treats of the value of the foodstuffs, proteins, fats, etc., in the diet, and the availability of these materials in various products. This section is of great importance to those who wish to understand thoroughly the subject of practical dietetics.

Part III takes up in a very satisfactory manner the troublesome question of feeding in infancy and childhood.

Part IV, devoted to feeding in disease, furnishes the major portion of the book. In these chapters the sound application of scientific knowledge to practical dietetics is the dominant note. Consequently, the author escapes many of the fallacies previously recorded, and succeeds in presenting a most useful and thoroughly up-to-date guide in this field. There is not an absolutely even distribution of effort among the various chapters, some subjects receiving more detailed attention than others.

BOOKS RECEIVED

Experiments with Oxygen on Disease; Tuberculosis, Bright's Disease, et al. By James Todd, A. M. 1916. 8°. 225 pages. Published by the author, Pittsburgh, Pa.

Diseases of the Chest and the Principles of Physical Diagnosis. By George William Norris, A. B., M. D. and Henry R. M. Landis, A. B., M. D. With a chapter on the Electrocardiograph in Heart Disease, by Edward B. Krumbhaar, Ph. D., M. D. 1917. 8°. 782 pages. W. B. Saunders Company, Philadelphia and London.

Technic of the Irrigation Treatment of Wounds by the Carrel Method. By J. Dumas and Anne Carrel. Authorized translation by Adrian V. S. Lambert, M. D., with an introduction by W. W. Keen, M. D., LL. D., F. R. C. S. (Hon.). 1917. 12°. 90 pages. Paul B. Hoeber, New York.

Food for the Sick: a Manual for Physician and Patient. By Solomon Strouse, M. D., and Maude A. Perry, A. B. 1917. 12°. 270 pages. W. B. Saunders Company, Philadelphia and London.

International Clinics. A Quarterly of illustrated Clinical Lectures and Especially Prepared Original Articles. By Leading Members of the Medical Profession Throughout the World. Edited by H. R. M. Landis, M. D. Volume IV. Twenty-seventh series. 1917. 8°. 314 pages. J. B. Lippincott Company, Philadelphia and London.

A Treatise on Regional Surgery. By Various Authors. Edited by John Fairbairn Binnie, A. M., C. M., F. A. C. S. Volume III. With 521 illustrations. 1917. 8°. 830 pages. P. Blakiston's Son & Co., Philadelphia.

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